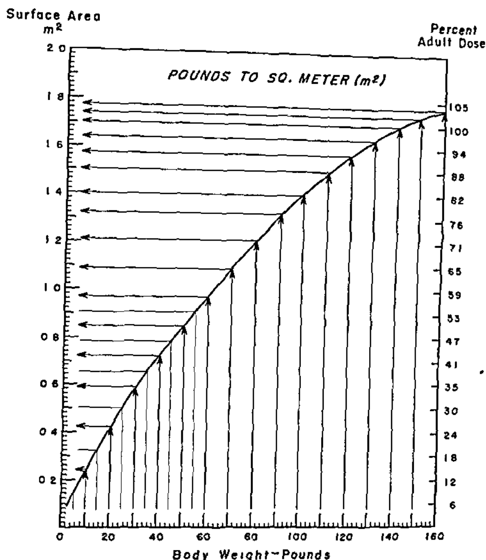
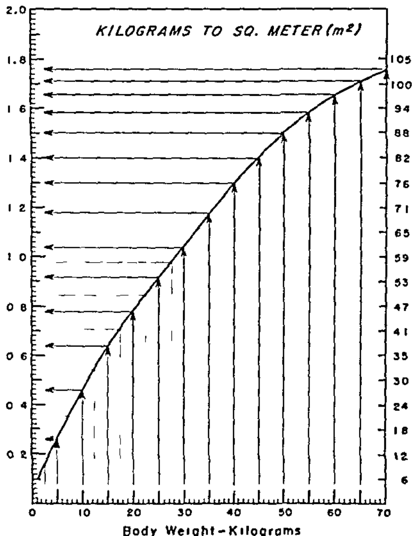


Graph A. Relations between Body Weight IN POUNDS, Body Surface Area and Adult Dosage

The surface area values correspond to those set forth previously (Crawford *et al* 1950) *Note that the 100 per cent adult dose is for an individual weighing about 140 pounds and having a surface area of about 1 7 m²*



Graph B. Relations between Body Weight IN KILOGRAMS, Body Surface Area and Adult Dosage

Except for the fact that the abscissal scale is in kilograms rather than pounds this graph is the same as that on the opposite page

Associate Professor of Pediatrics, Harvard Medical School
Physician, Children's Medical Service,
Massachusetts General Hospital

Instructor in Pediatrics, Harvard Medical School
Assistant Physician, Children's Medical Service,
Massachusetts General Hospital

Assistant Professor of Pediatrics, Harvard Medical School
Physician, Children's Medical Service,
Massachusetts General Hospital

Medical Artist,
Massachusetts General Hospital



METABOLIC HOMEOSTASIS

A Syllabus for Those Concerned with the Care of Patients

NATHAN B. TALBOT, M.D.

ROBERT H. RICHIE, M.D.

JOHN D. CRAWFORD, M.D.

EDITH S. TAGRIN

Published for The Commonwealth Fund
By Harvard University Press
Cambridge, Massachusetts · 1959

For approximately a quarter of a century THE COMMONWEALTH FUND, through

VARD UNIVERSITY PRESS became the publisher of Commonwealth Fund books, assuming responsibility for their production and distribution The Fund continues to sponsor and edit its books, and cooperates with the Press in all phases of manufacture and distribution

Published for The Commonwealth Fund by
Harvard University Press, Cambridge, Mass

Distributed in Great Britain by
Oxford University Press, London

Library of Congress Catalog Card No 59-14732
Manufactured in the United States of America

Acknowledgements

Many colleagues past and present have helped indirectly and directly in the preparation of this volume We are particularly indebted to Drs. Allan M Butler and E Eugene Yates for their many valuable suggestions and to Miss Gretchen Koch for her unstinting secretarial assistance

This work has been made possible by grants from the Commonwealth Fund of New York, by grants H 1529, A-808 and HTS-5139 of the National Institutes of Health, United States Public Health Service, and by the Medical Research and Development Board, Office of the Surgeon General Department of the Army, under Contract No DA-49-007-MD-437

In addition, we take particular pleasure in expressing our appreciation to the Division of Publications of the Commonwealth Fund for the interest and care taken in the publication of this volume

N B T

R H R.

J D C.

Table of Contents

Potassium Homeostatic System

Hydrogen Ion Homeostatic System

Chloride Homeostasis

Phosphorus Homeostasis

n B. Clinical Applications

Infant Feeding

Parenteral Fluid Therapy

Renal Disabilities

References

Conversion Charts

Explanatory Remarks on

Metabolic Homeostasis

Since Professor E H Starling of University College, London, and Professor W B Cannon of Harvard University first expressed admiration for the marvelous manner in which the organism can maintain a steady state through suitable adjustments, physiologists have gathered a vast amount of information concerning the "Wisdom of the Body" The present syllabus is concerned with the application of this information to the diagnostic and therapeutic problems faced by those responsible for the care of patients

The information presented here is basically very simple in nature Essentially, it is shown that the body contains a series of systems designed to keep body composition within normal limits Each system has a "sensing element' which detects abnormalities in the content or concentration of the substance for which it is responsible As directed by this element, the system acts to accumulate or eliminate the substance in accordance with homeostatic needs For the systems to accomplish these tasks, they must be provided with certain essential raw materials at adequate yet tolerable rates Most of the metabolic disturbances encountered clinically are due to failure to fulfill this important requirement Most subside spontaneously as soon as this need is met

Since it is as important for physicians to be familiar with the limits of capacity of the body s homeostatic systems as it is for surgeons to know the anatomy of the structures with which they are dealing, the first division of this syllabus will be concerned with descriptions of their functional characteristics in health and disease The second division of the syllabus then illustrates by specific clinical experiences the manner in which such information can be used to improve and at the same time to simplify patient care

The task of presenting this information in clinically useful form has been eased greatly by the fact that most body requirements, turnover rates and limits of tolerance *happen to be* approximately proportional to body "surface area" (i e to the two thirds power of body weight) This has

made it possible to express rates of intake and output for individuals of all ages and sizes with the aid of single per square meter (m^2) values instead of the multiple values needed when weight or "basal energy expenditure" estimates are used as the basis for calculations

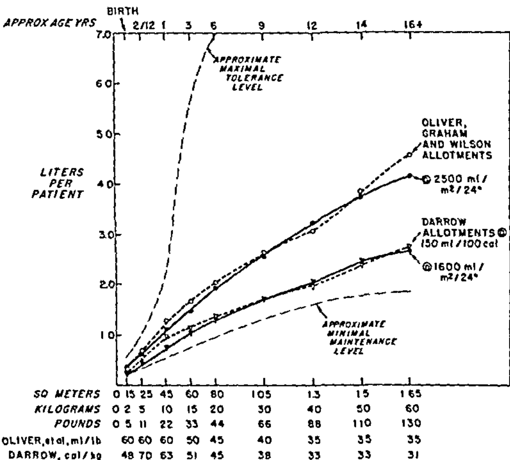
This may be visualized with the aid of the accompanying chart, which shows that fluid allowances, based on the series of milliliters per pound factors recommended by Oliver, Graham and Wilson,* correspond closely to a dosage of 2500 ml per m^2 per 24 hours Similarly, fluid allotments, calculated according to Darrow's recommendation that approximately 150 ml of water be given for each 100 calories of basal energy expended, differ little from those provided by prescribing 1600 ml per m^2 per 24 hours Incidentally, it is interesting to note that these authors differ by as much as 50 per cent in their recommended allowances The explanation for the fact that both regimens are well tolerated by normal individuals is to be found in the observation that both lie within the range of freedom of choice normally provided by the body's homeostatic systems In this chart this range corresponds approximately to the area defined by the minimal requirement and maximal tolerance levels shown near the bottom and the top of the chart

Surface area in square meters (m^2) can be estimated easily from body weight with the aid of the charts shown on the inside of the front cover The scale shown along the right-hand ordinate of these charts also indicates relations between body weight and drug dosage expressed as percentages of ordinary adult dosage values If desired, these can be used to convert adult values to per square meter values and vice versa While rates of intake and output, which are related to homeostatic function, are expressed per m^2 per unit of time, body content values, which are a function of mass, are expressed per kilogram of body weight

Though a number of the limits of tolerance indicated in this volume must be considered approximate where definitive data are scanty, nonetheless they have been found satisfactory in orienting clinical therapy It is to be hoped, however, that these first approximations may in due course be replaced with more refined data as physicians and physiologists continue their explorations of these vitally significant phenomena

While traditional methods of describing physiologic and medical phenomena usually are satisfactory, there are times when they may fail to place relationships in proper perspective Such appears to be the case with regard to the use of the term "milliosmoles per liter" in describing the

* Oliver Graham and Wilson s milliliters per pound factors and Darrow s factors for estimating basal energy output are set forth in the table at the bottom of the chart



Doses Based on Weight and on Basal Energy Expenditure in Relation to Per Square Meter Doses and Body Limits of Tolerance

function of the body's water homeostatic system This term appears to be the reciprocal of the variable with which this system actually is concerned, namely the ratio of water to solutes (i e milliliters per milliosmole) in body fluids Stated in other words, as individuals vary their fluid and food intake, this water system has the task of trying to prevent abnormal gains or losses of water relative to solutes, just as the various other homeostatic mechanisms strive to prevent pathologic gains or losses of the various sol utes for which they are responsible Accordingly, all water solute ratio values will be expressed as milliliters per milliosmole Those who wish to re express these values in terms of milliosmoles per liter can make the con version easily with the aid of graphs C and D (see inside back cover)

In choosing references for this syllabus, no attempt has been made to quote all the pertinent literature On the other hand an effort has been made to give the sources of the original data on which the charts and text are based as well as to indicate the titles of publications which have been found particularly useful as sources of additional information The com plete bibliography is listed alphabetically by authors at the end of the syllabus

References

Starling (1923) Homeostatic concepts
Talbot and Richie (1959) Use of surface area

SECTION A. BASIC CONSIDERATIONS

1. Body Content and Distribution of Water at Various Ages

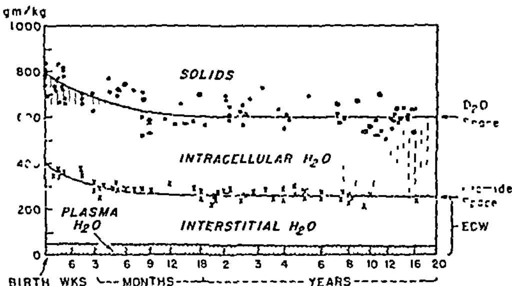
The accompanying chart shows the normal volume and distribution of the total body water at various ages These patterns are the product of recipro cal actions between the homeostatic systems which determine the electrolyte content of the body and the *neurohypophyseal–renal* system which normally keeps each milliosmole of solute encompassed by 3 5 to 3 7 ml of water* (chart 4)

As a result of changes in the "setting' of the systems responsible for body sodium and chloride homeostasis, interstitial fluid and hence total water content per kilogram of body weight commence to diminish early in the neonatal period, reaching adult levels at about nine months of age Possibly these changes are explained in part by the fact that newborn infants are slightly hypoalbuminemic in comparison with older infants and children This could predispose to the accumulation of extracellular fluid much as it does in nephrotic children (chart 44) In addition, the newborn *infant is apt to lose water out of proportion to solutes during the first two* or three days, when he is obliged to obtain from his body stores most of the water needed to compensate for insensible and urinary losses As a result, the water-solute ratio of body fluids decreases until water becomes available in the form of mother's milk or other fluid of low solute content

Technical Details

Solutes are the substances in solution in the body fluids They are made up of the various electrolytes and of other substances including glucose, amino acids, urea and creatinine One millimole of any of these substances in solution exerts one milliosmole of osmotic pressure This is distinct from the electrical potential which is measured in terms of milliequivalents The osmolar content of a solution can be determined by measuring its freezing point A depression of the freezing point by 1 86° C below that of pure water *signifies that there are* 1000 milliosmoles of solute in each liter of fluid

* For reasons mentioned under Explanatory Remarks this method of expression is used instead of the reciprocal namely 270 to 285 mosM per liter Those wishing to convert milliliters per milliosmole values to their milliosmole per liter equivalents can do so with the aid of the graph shown on the inside of the back cover



1. Body Content and Distribution of Water at Various Ages

Tracer doses of heavy water (D O) were used for determ ning total body water bromide was employed for measuring extracellular space and the dye T1824 for estimating plasma volume Solids were found as the d fference between total body water and body we ght and intracellular water as the d fference between extracellular volume and total body water D O probably g ves very accurate informat on about total body water Though bromide l ke chloride is located chiefly in extracellular

References

Brines *et al* (1941) Plasma volume data
Cheek (1954) Bromide space data (x)
Corsa *et al* (195( ) Total body water data (O)
Fris Hansen (1957) Total body water data (•)
Nichols *et al* (1953) Chloride space as measure of extracellular compartment

Components of Water Balance

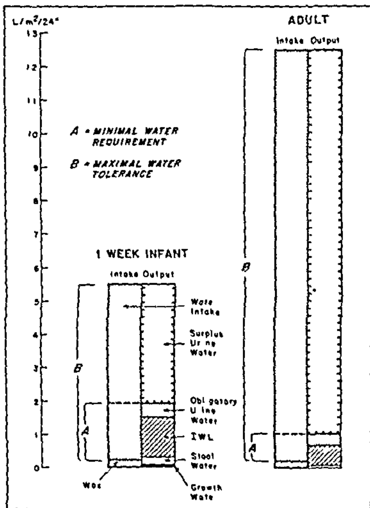
The water balance of the body fluctuates from positive to negative many times during the day as a consequence of the fact that the ingestion of water is intermittent Nevertheless, the organism usually is able to prevent major fluctuations in its water content by appropriate adjustments in rates of intake and output

As the accompanying diagram shows, except for the relatively small quantity of water formed during the process of oxidizing carbohydrate, fat and protein within the body (about 200 ml per m^2 per 24 hours) we are almost totally dependent upon exogenous water as a source of intake Under conditions of fasting, destruction of body protoplasmic tissues may yield a small additional volume (about 120 ml per m^2 per 24 hours)

Water is lost via a number of different routes Breast fed infants lose about 100 ml of water per m^2 per 24 hours in their stools On the other hand, infants fed cow's milk formulae and older persons taking ordinary diets lose only about 50 ml of water per m^2 per 24 hours by this route Though such losses may increase markedly, reaching levels of 500 ml per m^2 per 24 hours or more as a result of diarrhea, they are not subject to homeostatic control and therefore do not vary much under normal circumstances The same may be said of the water losses which take place through the skin and especially of those which take place through the lungs Though these vary somewhat with age and size and may be influenced by factors such as environmental temperature, clothing, humidity and body temperature, they tend to remain essentially constant under ordinary conditions of living in a temperate environment (chart 3)

The most important adjustments in the rate of water elimination are accomplished by the kidneys under the direction of the neurohypophysis (chart 4) The range over which this system normally can vary urinary output is indicated in chart 8

In the present chart minimal urine volume is indicated as "obligatory urine water," this being the smallest volume in which the kidneys can excrete the waste products presented to them for elimination Maximal urine volume is equal to the sum of the "obligatory urine water" plus the "surplus urine water " Viewed as a whole, the body's minimal water requirement is approximately defined by bracket A and its maximal water tolerance by bracket B



2 Components of Water Balance

The chart reproduced above shows the m n mal water requirement and the max mal water tolerance of a 1 week-old infant in comparison with those of an adult The following appropriate values have been used in construct ng the d agram selute

1 on is used in all the charts of the syllabus.

2. Components of Water Balance

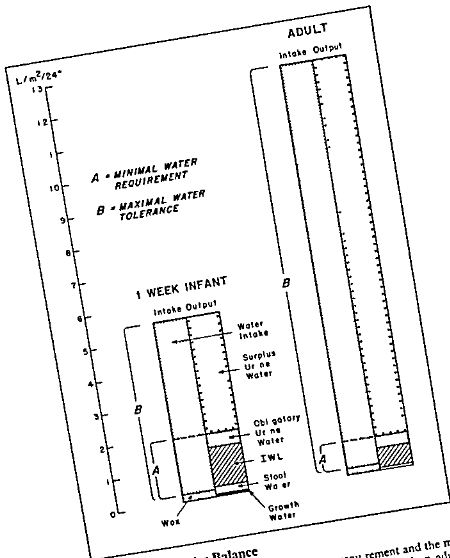
The water balance of the body fluctuates from positive to negative many times during the day as a consequence of the fact that the ingestion of water is *intermittent* Nevertheless, the organism usually is able to prevent major fluctuations in its water content by appropriate adjustments in rates of intake and output

As the accompanying diagram shows, except for the relatively small quantity of water formed during the process of oxidizing carbohydrate, fat and protein within the body (about 200 ml per m^2 per 24 hours) we are almost totally dependent upon exogenous water as a source of intake Under conditions of fasting, destruction of body protoplasmic tissues may yield a small additional volume (about 120 ml per m^2 per 24 hours)

Water is lost via a number of different routes Breast fed infants lose about 100 ml of water per m^2 per 24 hours in their stools On the other hand, infants fed cow's milk formulae and older persons taking ordinary diets lose only about 50 ml of water per m^2 per 24 hours by this route Though such losses may increase markedly, reaching levels of 500 ml per m^2 per 24 hours or more as a result of diarrhea, they are not subject to homeostatic control and therefore do not vary much under normal circumstances The same may be said of the water losses which take place through the skin and especially of those which take place through the lungs Though these vary somewhat with age and size and may be influenced by factors such as environmental temperature, clothing, humidity and body temperature, they tend to remain essentially constant under ordinary conditions of living in a temperate environment (chart 3)

The most important adjustments in the rate of water elimination are accomplished by the kidneys under the direction of the neurohypophysis (chart 4) The range over which this system normally can vary urinary output is indicated in chart 8

In the present chart minimal urine volume is indicated as "obligatory urine water," this being the smallest volume in which the kidneys can excrete the waste products presented to them for elimination Maximal urine volume is equal to the sum of the "obligatory urine water" plus the "surplus urine water " Viewed as a whole, the body's minimal water requirement is approximately defined by bracket A and its maximal water tolerance by bracket B



2 Components of Water Balance

The chart reproduced above shows the minimal water requ rement and the maximal water tolerance of a 1 week-old infant in comparison with those of an adult The following appropriate values have been used in constructing the d agram solute load of 250 mosM/m /24 hours for both infant and adult maximal urine concen tration of 1 7 ml/mosM for the infant and of 1 6 ml/mosM for the adult (conserva tive est mates) max mal urine d lution of 16 ml/mosM for the infant and of 50 ml mosM for the adult Wox — water of oxidat on IWL = insens ble water loss L/m²/24° — l ters per square meter per 24 hour period This form of abbrevia on is used in all the charts of the syllabus.

References

Ames (1953) Infant s maximal water tolerance
Gamble (1958) General
Hansen and Smith (1953) Infant s minimal water requirement
Newburgh *et al* (1945) Water of oxidation
Shohl (1939) General

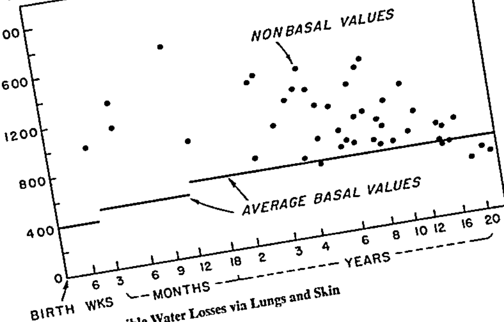
3. Water Losses via Lungs and Skin

Infants, children and adults have approximately similar basal rates of insensible water loss via the lungs and skin However, basal conditions apply only to that small segment of the day when the individual is at rest Rates of loss are apt to be greater during periods of activity Consequently, except in persons living an inactive existence, total daily losses exceed the basal rate by a considerable margin These total losses may be higher in infants (average, 1200 ml per m^2 per 24 hours) than they are in children (average, 1000 ml per m^2 per 24 hours) or adolescents and adults (average, 700 ml per m^2 per 24 hours)

The rate at which water is lost insensibly may become reduced al most to zero when the humidity is raised to 100 per cent as in a croup tent Contrariwise, insensible water losses are higher when individuals are nude and can be doubled by the hyperpnea of diabetic ketoacidosis or salicylate intoxication In addition to the water lost insensibly, individuals can lose a liter or more per day in the form of sweat, if they become overheated

Because the neurohypophyseal-renal system can compensate for moderate fluctuations in insensible water losses by appropriate adjustments of urinary output, in estimating body water requirements and tolerances it suffices under most circumstances to assume that losses via the lungs and skin amount to about 1000 ml per m^2 per 24 hours It is important, however, to make a closer estimate of water losses via these routes when a patient s homeostatic capacity (chart 45A) has become markedly reduced, as in pannephritic or anuric individuals or when it is obvious that the individual is sweating profusely

References



3. Insensible Water Losses via Lungs and Skin

4. Water Homeostatic System

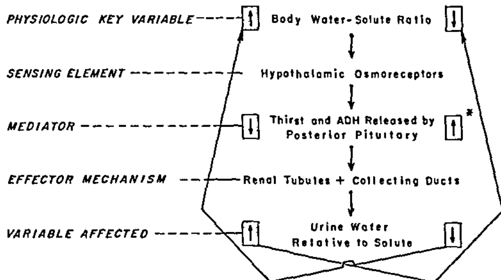
The neurohypophyseal–renal *or water homeostatic system is designed to* keep the ratio of water to solutes* in body fluids within the range of 3 5 to 3 7 ml for each milliosmole This is an important physiologic variable because elevation of the water solute ratio by as little as 10 per cent to 3 9 or 4 0 ml per mosM is apt to result in water intoxication Contrariwise, reduction of the ratio by 5 or 10 per cent to 3 3 ml per mosM, or less, tends to produce symptoms and signs of hypohydration (chart 7)

The system functions somewhat like a feedback circuit A tendency to abnormal lowering of the ratio of water to solutes in body fluids is recognized by osmoreceptors located in the hypothalamus As the ratio falls, they respond by creating a sensation of thirst (chart 45C) and by causing the neurohypophysis to secrete antidiuretic hormone into the blood stream † The renal tubules react to this hormone by reducing the quantity *of water accompanying each milliosmole of solute in the urine* Passage of urine, which is so concentrated that it contains less water for each milliosmole of solute than the plasma from which it was derived, tends to raise the water solute ratio of the body fluids When this approaches a physiologically satisfactory level, the sensation of thirst abates and the secretion of antidiuretic hormone ceases On the other hand, the reverse of these homeostatic reactions follows an abnormal rise in the water solute ratio of the body fluids Then the ratio in the body fluids falls as the ratio in the urine rises

The water homeostatic system, while closely concerned with the stability of the water solute ratio of body fluids, also is involved in the preservation of a satisfactory vascular volume Available evidence suggests that there are stretch or pressure sensitive elements, possibly located in the left atrium, which can *promote thirst and antidiuretic hormone production* irrespective of the water solute ratio of body fluids should the vascular volume become abnormally reduced In patients suffering from blood loss, *hypoalbuminemia or extracellular* electrolyte deficiency, this response can

convulsions (chart 42)

* Exclusive of urea



* This mechanism also may be activated by hypovolemia

4. Water Homeostatic System

References

Smith (1957) General
Talbot *et al* (1952) General
Verney (1957) General

5. Dynamics of Water Homeostasis

As the accompanying chart demonstrates, the water homeostatic system normally reacts so nimbly to changes in intake that one can suddenly vary the intake rate all the way from the physiologic minimal to the physiologic maximal level without disturbing body water status (i e serum ml/mosM) to a major extent

There is apt to be a lag of approximately 45 minutes between the time when water load is first imposed and the time when urine water solute ratio and hence urine flow values commence to increase Nonetheless, adaptation is essentially completed within 2 hours The same is true when the water intake rate is reduced suddenly from a high to a low level

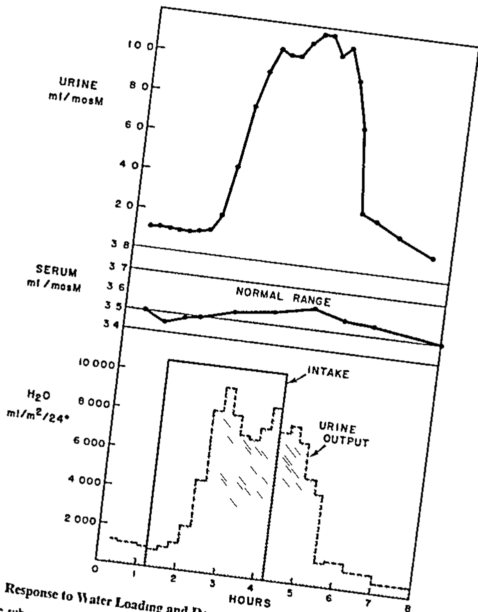
Reference

Crawford *et al* (to be published) General

6. Demonstration of Maximal Tolerance and Minimal Requirement for Water

As has been mentioned in preceding sections, there are limits to the body's capacity to conserve and to eliminate water in accordance with needs More specifically, there is a *physiologic minimal requirement, or floor*, which represents the lowest rate of intake required to balance output and hence to prevent deficits when conservation forces are acting maximally *Similarly, there is a physiologic maximal tolerance, or ceiling*, which represents the largest amount of water that can be taken and eliminated per unit of time without seriously disturbing body composition Rates of intake and output falling between these two extremes lie in what may be called the *effective or safe working range* of homeostatic function

The subject of the accompanying chart was a 20-year-old youth with marked impairment of renal function, as evidenced by the fact that his urea clearance was *only 5 per cent of normal In the left-hand set of* diagrams, it can be seen that his serum water-solute ratio was abnormally elevated when first measured This meant that he had at that time a strong need to raise his urine water solute ratio to the highest level of which he was capable Accordingly, the urine water-solute ratio value found *at that time*, namely 7 ml per mosM, could be considered his ceiling value At



5. Response to Water Loading and Deprivation

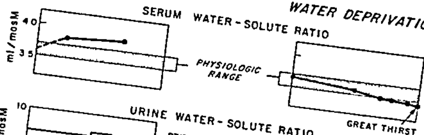
The subject for the water loading experiment was a healthy young man who was given water orally at 15 minute intervals

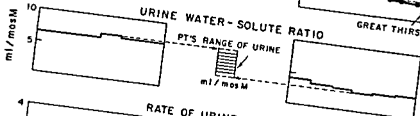
his average rate of solute output (285 mosM per m^2 per 24 hours), this meant that he could not excrete more than 285 x 7, or about 2000 ml of urine per m^2 per 24 hours His upper limit of body tolerance for water, estimated by adding to this maximal urine value an approximate value for insensible water losses minus water of oxidation (i e 1000–200, or 800 ml per m^2 per 24 hours), was found to be 2800 ml per m^2 per 24 hours

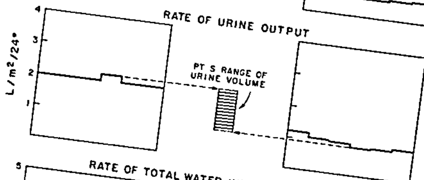
Inasmuch as he was already "over ceiling" with respect to rate of water intake when these measurements were made, there was no need to subject him to an additional water load in order to demonstrate where his ceiling was located On the other hand, it was necessary to restrict his water intake for a limited period in order to determine his minimal water requirement As can be seen in the right hand diagrams, thirsting caused his serum water-solute ratio values to fall rapidly to subnormal levels When this occurred, the neurohypophyseal system caused the urine water-solute ratio to fall to the lowest level possible, namely 2 5 ml per mosM This meant that while he was excreting solutes at the rate of 285 mosM per m^2 per 24 hours, his minimal urinary output would be 285 x 2 5, or about 700 ml per m^2 per 24 hours It followed that his over-all minimal water requirement, estimated as outlined above, was approximately 1500 ml per m^2 per 24 hours Thus, these observations indicated that, provided there was no change in total solute output, he should take at least 1500 but not more than 2800 ml of water per m^2 per 24 hours in order to avoid hypohydration on the one hand and hyperhydration on the other

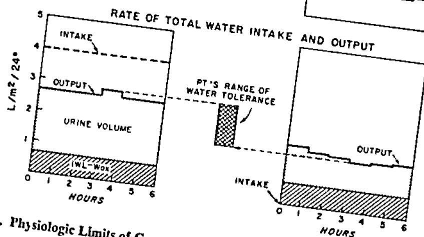
Reference

Kerrigan *et al* (1955) Source of data









6. Physiologic Limits of Capacity to Conserve and Eliminate Water

7. Symptoms and Signs of Water Deficit and Excess Relative to Solutes

Lowering of the ratio of water to solutes (other than urea) in body fluids below 3 5 ml per mosM results in thirst, concentration of the urine and, provided the solute output rate is not very high, a tendency to oliguria Lowering of the water-solute ratio below 3 2 ml per mosM is apt to result in fever Extreme lowering to levels below 2 9 ml per mosM can lead to central nervous system disturbances with lethargy, irritability, twitching, electroencephalographic changes, acidosis, respiratory or circulatory failure and death *

When such hypohydration (i e low water solute ratio) is due simply to lack of water relative to solutes, the concentrations of sodium and chloride are apt to be increased in proportion to the increases in concentration of all other solutes Under such circumstances, serum sodium and chloride concentration measurements may serve as inverse indices of water-solute status Hence, it is not uncommon to find the serum sodium concentration elevated to 170 and the serum chloride to 130 mEq per liter, *or higher, in patients with* serum *water-solute* ratio values in the neighborhood of 2 9 ml per mosM The serum sodium and chloride values may not be elevated, however, in patients who become hypohydrated as a result of the accumulation in body fluids of many milliosmoles of ketone bodies (chart 40A) or other unusual solutes It follows that the finding of normal serum sodium and/or chloride concentration values does not rule out hypohydration Neither does the presence of gross edema, for patients with large accumulations of tissue fluid may have even larger accumulations of solutes *and therefore* may suffer from lack of water in proportion to solutes This condition occurred commonly during the days when it was customary to treat patients with fluids of relatively low free-water content such as isotonic saline

Elevation of the water-solute ratio in body fluids to 4 ml per mosM of *non urea solutes is apt to result in* headache, confusion, nausea, weakness, cramps, convulsions, coma and other manifestations of water *intoxication, if it occurs rapidly* in the course of a few hours On the other hand, very gradual elevation of the water solute ratio to equally high levels, as sometimes occurs in patients with nephrosis or pannephritis, may not produce overt signs

* Such signs of dehydration as loss of subcutaneous tissue elasticity and softness of eyeballs are seen only if the total body water is subnormal

The elevation in water solute ratio responsible for signs of water intoxication may occur as a result either of an absolute gain in water relative to solutes or an absolute loss of solutes relative to water or both (chart 42A) Hence, water-intoxicated persons do not necessarily show signs of water surplus such as edema The character and volume of the urine also may vary widely under different circumstances If the patient is suffering simply from an overload of plain water, he will put out large volumes of maximally dilute urine (chart 8) On the other hand, if he is suffering from hypovolemia, heart failure or the effects of various other factors which can result in the uncontrolled release of antidiuretic hormone, the urine will tend to be highly concentrated and of small volume (chart 42A) Even if the urine is maximally dilute, the volume may not be very great unless there is a generous solute output (chart 47)

As in hypohydration, serum sodium and chloride concentration values tend to fall as the water solute ratio of the plasma rises On the other hand, they may become lowered as the result of the fact that other substances such as ketone bodies, glucose and bicarbonate have accumulated in body fluids It follows that the diagnosis of water deficit or excess relative to solutes in body fluids can be made most dependably by direct measurement of the total solute content as revealed by freezing point depression or other suitable index

Symptoms and Signs of Water Deficit and Excess Relative to Solutes

TOO LITTLE

Thirst
Concentrated urine
Oliguria
Fever
Irritability
Lethargy
Muscle twitching
Electroencephalographic changes
Acidosis
Respiratory or circulatory failure
Serum water solute ratio
 < 3 5 ml per mosM,
 serum solutes > 285
 mosM per liter

TOO MUCH

Headache
Confusion
Nausea
Vomiting
Weakness
Muscle twitching and cramps
Electroencephalographic changes
Convulsions
Coma
Serum water-solute ratio
 > 3 7 ml per mosM,
 serum solutes < 270
 mosM per liter

References

Crawford and Dodge (1959) General
Sotos *et al* (to be published) Water deficit
Weil and Wallace (1956) Water deficit
Wynn (1956) Water excess

8. Normal Ranges of Renal Capacity to Vary Urine Water-Solute Ratio and Urine Volume at Various Rates of Solute Output

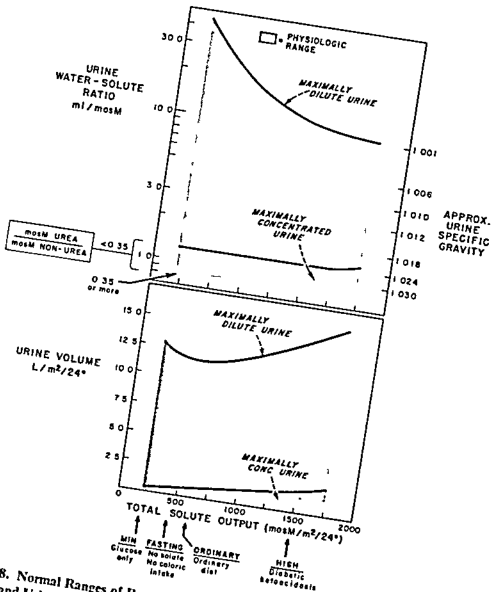
The upper curves of the accompanying diagrams represent physiologic maximal values and the lower curves physiologic minimal values. It can be seen that the kidneys' ability to dilute the urine is greatest at low rates of solute output and least at high rates of solute output. Maximal rates of urine flow, calculated by multiplying these maximal values for urine water-solute ratio by the corresponding values for rate of solute output, start at about 12.5 liters per m^2 per 24 hours and increase to about 15 liters per m^2 per 24 hours at high rates of solute output.

These ceiling levels are so high that normal individuals rarely reach them. For instance, an adult weighing 70 kg would have to drink more than 5 gallons of water per 24 hours, or about one 250 ml tumbler every 15 minutes to overload the renal excretory mechanism.

Renal ability to concentrate urine in response to full antidiuretic hormone stimulus usually is not influenced very much by variations in rates of solute output.* Concentrating capacity increases, however, as the ratio of urea to other solutes in the urine approaches 0.35. *At this osmolar ratio,* the kidneys can reduce the water content of the urine to 0.7 ml per mosM (specific gravity 1.030). If the proportion of urea to other solutes is much less than this value, the kidneys may not be able to reduce the water-solute ratio of the urine below 1.5 ml per mosM.

Patients also suffer partial loss of concentrating ability when their cellular potassium stores become depleted and are replaced by sodium (chart 19). Except for these factors, minimal urine volume varies directly with rate of solute output. It amounts to about 150 ml per m^2 per 24 hours at the minimal rate of solute output (i.e. 200 mosM per m^2 per 24 hours) found in persons taking 100 gm of glucose per m^2 per 24 hours together with an adequate quantity of water. It increases to about 275 ml per m^2 per 24 hours in fasting individuals, who are apt to excrete about 375 mosM of solutes per m^2 per 24 hours. Healthy persons eating a normal diet excrete 500 to 600 mosM of solutes per m^2 per 24 hours and hence have a minimal urine volume of 350 to 450 ml per m^2 per 24 hours. In patients whose solute output has risen to exceptionally high levels (i.e.

* [illegible] ence at very high rates of output when [illegible] lute number of solutes [illegible] ning nephrons. Hence, [illegible] rmal persons



8. Normal Ranges of Renal Capacity to Vary Urine Water-Solute Ratio and Urine Volume at Various Rates of Solute Output

about 1500 mosM per m^2 per 24 hours) as a result of burns, other severe trauma or the glycosuria and ketonuria of diabetic ketoacidosis, minimal urine volume may amount to 2000–3000 ml per m^2 per 24 hours

References

Crawford *et al* (to be published) Source of data
Talbot *et al* (1955) General

9. Normal Limits of Total Body Tolerance for Water

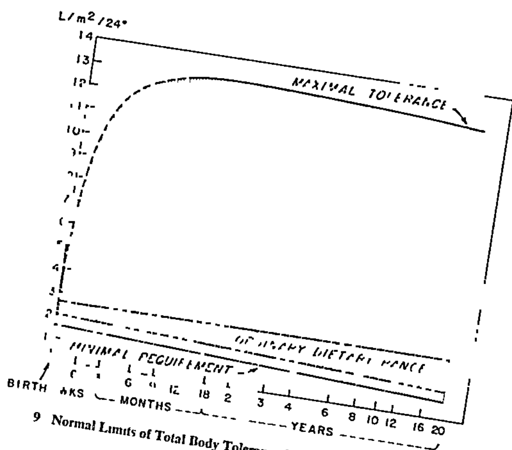
Using the data presented in charts 2, 3 and 8, one can make approximate estimates of the maximal water tolerance and minimal water requirements of healthy individuals of various ages The limited information available indicates that because renal function is immature at birth infants have much less ability to diurese during the first days of life than they will after reaching four weeks of age Hence, the relatively low maximal water tolerance levels shown for the neonatal period Older individuals can tolerate as much as 12 to 13 liters per m^2 per 24 hours

Because infants are apt to have larger insensible water losses per m^2 per 24 hours than children and adults, their minimal water requirements amount to about 1 6 liters per m^2 per 24 hours as compared with an adult's requirement of about 1 liter per m^2 per 24 hours These minimal requirements increase by 200 to 500 ml per m^2 per 24 hours if the infant is fed a cow's milk formula instead of human milk or if the adult eats a diet of ordinary rather than exceptionally low solute residue

Healthy persons can safely vary their water intake from 1500 to 12000 ml per m^2 per 24 hours under ordinary circumstances These limits may become narrowed by certain conditions, including the following

CEILING LOWERED
General anesthesia (chart 42A)
Morphine-type drugs (chart 42A)
Pannephritis (chart 45A)
Diseases which transect the blood brain barrier in the region of the hypothalamus (chart 42A)
Hypovolemia or circulatory failure (charts 4, 42, 44D)
Neonatal period

FLOOR RAISED
Pitressin deficiency (diabetes insipidus)
Pitressin resistance (renal diabetes insipidus) (chart 47A)
Cellular potassium insufficiency plus sodium intoxication (chart 19)
Pannephritis (chart 45A)



9 Normal Limits of Total Body Tolerance for Water

References

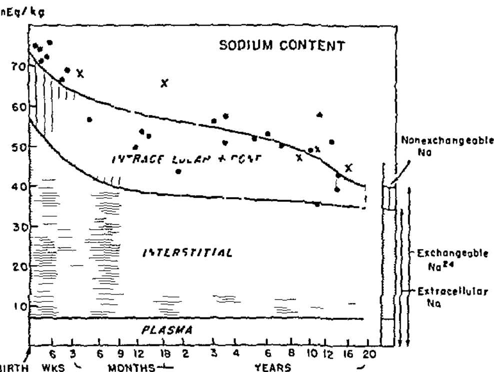
Ames (1953) Infant s maximal water tolerance
Crawford *et al* (to be published) Minimal and maximal urinary output
Hansen and Smith (1953) Infant s minimal water requirement
Heeley and Talbot (1955) Insens ble water loss
Macy (1942) Normal water intake
Shohl (1939) General

10. Body Content and Distribution of Sodium at Various Ages

Newborn babies have about 35 per cent more sodium for each kilogram of body weight than 1 year old infants and about 65 per cent more than adults Most of the infants' "extra' sodium is dissolved in the interstitial fluids at a concentration of *approximately 140 mEq per liter Though the* body's sodium is largely stored outside the cells, between 15 and 25 per cent is located within the cells and in bones Like the extracellular sodium, most of this intracellular sodium exchanges readily with tracer doses of *the radioactive isotope* Na^{24} and hence is presumed to be readily available for metabolic processes

The accompanying chart is based primarily on values for total exchangeable sodium per kg of body weight as determined with tracer doses of Na^{24} The curve depicting the total exchangeable content is based on a formula proposed by Forbes and Perley The portion of this sodium which is located in the plasma and interstitial fluid was estimated by multiplying the plasma and interstitial volume values shown in chart 1 by a representative value for the concentration of sodium in an ultra filtrate of serum (i e 143 mEq per liter) Of the remaining sodium, about 2 5 mEq per kg are situated in protoplasmic cells at a concentration of approximately 8 mEq *per liter and the rest is present in bone matrix*

References



10 Body Content and Distribution of Sodium at Various Ages

- • data of Forbes and Perley (1951)
- x data of Corsa *et al.* (1956)

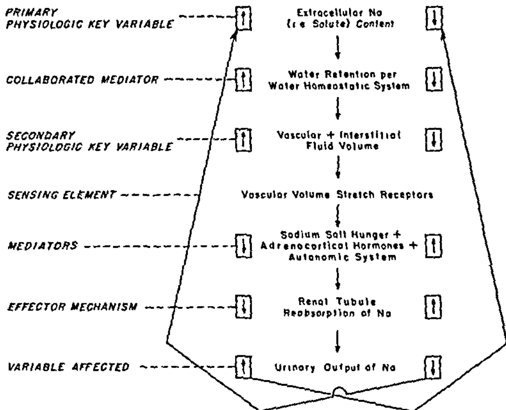
11. Sodium Homeostatic System

The sodium *homeostatic system normally plays a major part* in maintain ing vascular volume at physiologically satisfactory levels It accomplishes this task by functioning in a coordinated manner with certain other home ostatic mechanisms

A decrease in the body s sodium content results in a diminution in extracellular solute content To maintain body water solute ratio values at normal levels the water homeostatic system (chart 4) eliminates about 7 2 ml of extracellular water for each milliosmole of sodium lost Of this total 3 6 ml are accounted for by the sodium itself and 3 6 ml by the chlo ride bicarbonate and other anionic solutes which necessarily accompany sodium in extracellular fluid Such loss of extracellular fluid reduces plasma volume and hence blood volume The tendency to hypovolemia is detected by pressure or volume sensitive elements in the region of the carotid sinus *These elements probably act indirectly by means of the adrenocortical*– aldosterone mechanism and directly via neurologic pathways to cause the kidneys and sweat glands to conserve sodium They also may create a craving for salt which predisposes to increasing the sodium chloride in take For each milliosmole of sodium gained as a consequence of these re actions the neurohypophyseal system accumulates about 7 2 ml of water Because a portion of this newly formed extracellular fluid is attracted to the vascular compartment by plasma albumin the blood volume is in creased As this reaches satisfactory levels the stimulus for sodium con servation wanes and equilibrium is re established The reverse of these changes occurs when the body s sodium content rises above normal levels

References

Barger *et al* (1959) Neural control of Na excret on
Leaf *et al* (1953) Vascular volume and Na excretion
Selkurt (1954) General
Sm th (1957) General

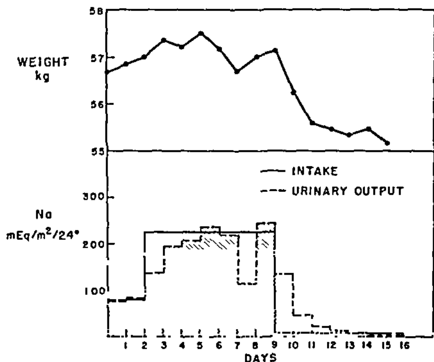


11. Sodium Homeostatic System

12. Dynamics of Sodium Homeostasis

When the sodium intake is increased abruptly, there may be a lag of one or more days before the urinary output of sodium increases to the point where equilibrium is re established The sodium accumulated during this interval leads to the retention of a physiologically equivalent volume of water, with resultant weight gain, and at times even to visible edema formation Provided the maximal capacity of the organism to eliminate sodium has not been over reached, most of this surplus sodium and its accompanying anions and water are unloaded eventually

The healthy organism reacts to sudden restrictions of sodium intake within a day and can reduce its rate of sodium loss almost to nil within three or four days



12. Dynamics of Sodium Homeostasis

The source of the data in the above chart was a healthy young woman on a constant normal diet who ingested added NaCl during the loading period and then changed to a low sodium diet on day 9

13. Symptoms and Signs of Sodium Deficit and Excess

Most of the symptoms and signs in the accompanying list are explained by the changes in extracellular fluid volume, which usually take place as extracellular sodium stores become abnormally depleted or expanded As extracellular fluid diminishes, circulatory collapse is prevented up to a point *by the transfer of water from the interstitial to the vascular* compartment and by compensatory reduction in the size of the vascular bed When further contraction becomes impossible, signs of circulatory failure are apt to develop rather abruptly (chart 14) They can be made to disappear by giving enough extracellular type fluid to expand vascular volume above the critical level

On the excess side, rapid intravenous administration of sodium, in the form of an extracellular type fluid such as isotonic saline, can lead to overexpansion of vascular volume and hence to congestive heart failure even in healthy individuals On the other hand, if the load is imposed more slowly and the organism has time to transfer surplus extracellular fluid into the interstitial spaces, surplus sodium is likely to show up as edema fluid Experience with nephrotic and cardiac patients indicates that double, triple and even quadruple the normal amount of sodium may be stored in the body as edema fluid without catastrophic results There comes a point however, where edema may so embarrass respiratory and other functions that it is incompatible with life Sodium also can accumulate in excessive quantities in the cells of individuals with potassium insufficiency and give rise to the *cellular potassium lack–sodium intoxication* syndrome (chart 19)

Serum sodium concentration cannot be considered a reliable index of body sodium status Rather it constitutes an inverse index of the water-solute ratio of body fluids A high serum sodium concentration usually *means that there is too little water in proportion to solutes in the body* fluids, not that there is too much sodium in the body Conversely, a low serum sodium concentration usually* signifies that there is a surplus of water in proportion to solutes in the body, only occasionally is there an associated absolute sodium deficit

It follows that one must judge body sodium status clinically either by means of isotopes, which are not generally available, or by estimating vas

* *In lipemic patients* though the concentration of sodium per liter of serum may be abnormally low its concentration per liter of serum *water* may be within normal limits

cular and interstitial fluid volume The occurrence of signs of hypovolemia or of interstitial dehydration in an individual with a normal or subnormal serum sodium concentration is indicative of sodium deficit (charts 14, 36) Conversely, the existence of signs of hypervolemia or of interstitial edema in an individual whose serum sodium concentration is not grossly depressed ordinarily means that the sodium content of the body is greater than normal In judging body sodium status it is well to remember that extracellular sodium deficit is only one of a number of factors, including hemorrhage, hypoalbuminemia and certain forms of heart failure, which may act to reduce vascular volume and/or pressure in the region of the carotid sinus and thereby cause the body to retain sodium and form extracellular fluid Unless this extracellular expansion "satisfies" the sensing element, the tendency to fluid retention is apt to persist and to result in the development of edema

Symptoms and Signs of Sodium Deficit and Excess

TOO LITTLE	TOO MUCH
Dehydration	Hypertension
Loss of tissue elasticity	Edema
Soft eyeballs	Congestive heart failure
Microcardia	See also the cellular potassium lack–sodium intoxication syndrome (chart 19)
Tachycardia	
Hypotension	
Hemoconcentration	
Prerenal azotemia	
Tendency to water intoxication	
Circulatory failure	

References

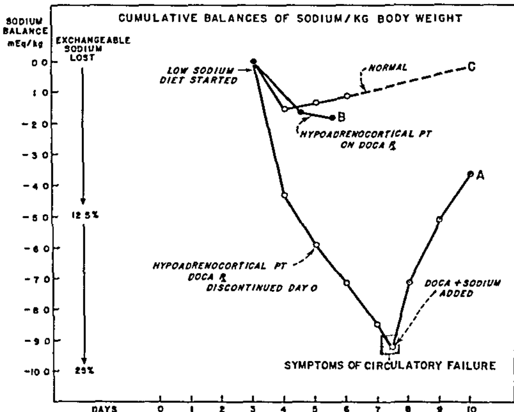
Elkinton and Danowski (1955) General
Talbot *et al* (1952) General

14. Development and Recovery from *Sodium Insufficiency*

The data in the accompanying chart were obtained in the case of a 13-year old boy whose desoxycorticosterone therapy was discontinued on day zero and whose sodium chloride intake was reduced on the third day to a low level (*i e 10 mEq per m^2 per 24 hours*) for the purpose of certifying a tentative diagnosis of adrenocortical insufficiency (line A) Following this, he lost almost 9 mEq of sodium per kg, or about 20 per cent of his body's stores, together with a proportional quantity of extracellular fluid before he developed overt signs of circulatory insufficiency. Then, rather abruptly he became weak and hypotensive, developed a rapid, thready pulse and appeared to be on the verge of circulatory collapse These manifestations disappeared as soon as the patient was given 1 mEq of sodium per kg in the form of isotonic saline He remained symptom free throughout the remainder of the several days when he was replenishing his stores

The fact that it was not necessary to correct his body sodium deficit by more than one ninth part in order to eliminate most of the clinical signs of deficiency is worthy of note This seems to be generally true of many situations Thus, though it may be important to raise the body content of depleted patients promptly above the critical symptomatic level, it is not necessary or perhaps even desirable to attempt to repair deficits in toto within a few hours Once the critical level has been passed, patients usually do well if allowed to correct their residual metabolic disturbances in *a smooth, asymptotic manner*

The present chart also is of interest in that it demonstrates that this same patient, when given desoxycorticosterone, could conserve sodium under conditions of low salt intake (line B) almost as efficiently as a normal person (line C)



14. Development and Recovery from Sodium Insufficiency

The source of the data in the above chart was a patient with hypoadrenocorticism (curve A) whose desoxycorticosterone acetate therapy was stopped on day 0 and whose sodium intake was reduced to 10 mEq per m² per day on day 3. The interval during which he manifested symptoms and signs of circulatory insufficiency is represented by the shaded area. Curve B shows how the patient of curve A responded to the low sodium regimen when being treated with DOCA. Curve C indicates the response of the normal individual to sodium restriction.

15. Normal Limits of Body Tolerance for Sodium

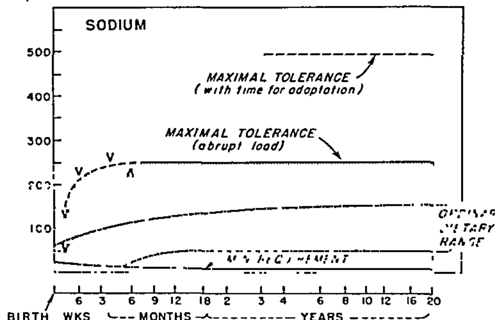
The scanty data available suggest that newborn infants are unable to take as much sodium as older infants, children and adults without becoming edematous Healthy children and adults usually can take and eliminate up to 250 mEq per m per 24 hours without difficulty Moreover, they may be able to manage loads of 500 or more mEq per m^2 per 24 hours if their sodium intake is increased gradually in a manner which provides ample time for adaptation In these connections, it is important to remember that tolerance even for moderate amounts of sodium is contingent upon having at least a moderate potassium intake

Because the kidneys and sweat glands can reduce the rate of sodium output almost to zero when conservation forces are acting maximally, the body can maintain its sodium balance on an intake of less than 10 and maybe less than 5 mEq per m^2 per 24 hours This means that if one wants to prevent sodium retention and edema formation in a cardiac or nephrotic patient, it is necessary to restrict the salt intake drastically

Among the conditions which may shift the limits of tolerance for sodium, the following may be mentioned

CEILING LOWERED
Zero potassium intake
Hypoalbuminemia (charts 44B, 44C)
Cardiac failure
Severe stress
Corticosteroid therapy
Cushing's syndrome
Renal disease

FLOOR RAISED
[illegible]
[illegible])
[illegible]
[illegible]
Renal tubule disease
Treatment with acetazoleamide, mercurial and other diuretics



15. Normal Limits of Body Tolerance for Sodium

Range of tolerance for sodium from birth to adulthood V indicates observed intakes above maximal tolerance A indicates observed tolerable intake

References

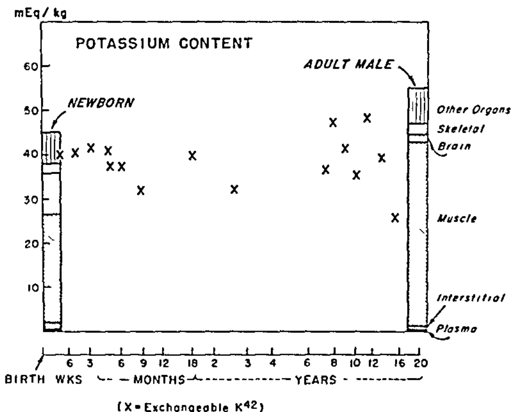
Darrow and Pratt (1950) Floor values
Gamble (1946–47) Adult floor values
Gamble *et al* (1951) Infant ceiling values
Leaf *et al* (1949) Adult ceiling values
Macy (1942) Ordinary sodium diet
McCance and Widdowson (1957) Infant ceiling values
Shohl (1939) Ordinary sodium diet
Smith (1958) Infant ceiling values
Stewart and Rourke (1942) Adult ceiling values
Talbot *et al* (1952) Adrenocortical relations

16. Body Content and Distribution of Potassium at Various Ages

The body normally contains between 45 and 55 mEq of K^{39} per kg of body weight at all ages Most of this exchanges readily with its radioactive isotope, K^{42}, which can therefore be used to measure the size of body potassium stores Potassium is located chiefly in protoplasmic cells at a concentration of about 150 mEq per liter of cell water In the newborn infant about 60 per cent of this potassium is located in the musculature and about 20 per cent in the brain, the rest being divided among extracellular fluid, the skeleton and other organs In the adult the musculature contains about 80 per cent of the body's total potassium content, the remainder being distributed more or less evenly among extracellular fluid, brain, skeleton and other structures

References

Corsa *et al* (1956) Exchangeable K' data
Elkinton and Danowski (1955) General
Shohl (1939) Carcass analysis data



16. Body Content and Distribution of Potassium at Various Ages

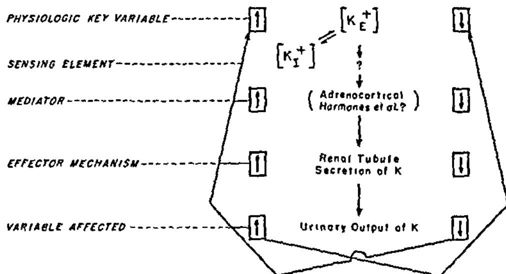
17. Potassium Homeostatic System

Though certain of the salient characteristics of this system can be discerned and described, many important details remain to be clarified It is clear that serum potassium concentration is one physiologic key variable worthy of note, for hyperkalemia per se results in various manifestations of potassium intoxication as described in the text accompanying chart 19 Moreover, it acts in some way, possibly in part via adrenocortical hormones, to stimulate excretion of potassium by the renal tubules into the urine *

Cellular potassium status is another variable which the body attempts to defend with considerable vigor Though the cells can store surplus potassium in amounts equaling between 5 and 10 per cent of their normal content (i e about 3 mEq per kg of total body weight), the organism normally eliminates such excess cellular potassium by way of the kidneys within a few hours, thereby rendering the cells capable of buffering a potassium load once again The adrenal cortices play an essential role in this reaction The capacity to store surplus potassium temporarily within body cells constitutes a valuable defense against dangerous degrees of hyperkalemia and gives us the ability to handle much larger loads of potassium than would be the case if we had to depend exclusively upon the renal excretory mechanism to prevent hyperkalemia

Hypokalemia per se does not necessarily result in maximal conservation of potassium by the kidneys *On the other hand depletion of cellular* potassium stores usually does lead to conservation of this ion by the kidneys However, the body is unable to conserve cellular potassium stores when deprived of potassium unless the sodium intake also is restricted sharply This is a fact of considerable clinical significance, for it means that one may be causing patients to develop cellular potassium insufficiency when one maintains them on potassium free, sodium rich solutions such as isotonic saline Fortunately this danger can be minimized by providing both sodium and potassium in physiologically tolerable amounts

* This is accomplished in large part at least by exchanging potassium ions within the cells of the renal tubules for sodium ions present in the tubular fluid It probably explains why it is necessary to take at least moderate amounts of sodium in order to excrete large amounts of potassium by way of the kidneys



17. Potassium Homeostatic System

References
Berliner (1952) General
Berliner *et al* (1950) General
Drescher *et al* (1958) Storage of surplus K^+
Laragh and Stoerk (1957) Effect of serum potassium on aldesterone excretion
Spater *et al* (1959) Potassium deficiency

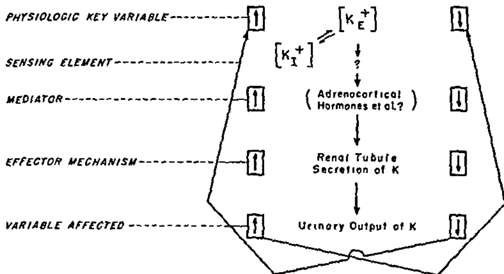
17. Potassium Homeostatic System

Though certain of the salient characteristics of this system can be discerned and described, *many important details remain to be clarified* It is clear that serum potassium concentration is one physiologic key variable worthy of note, for hyperkalemia per se results in various manifestations of potassium intoxication as described in the text accompanying chart 19 Moreover, it acts in some way, possibly in part via adrenocortical hormones, to stimulate excretion of potassium by the renal tubules into the urine *

Cellular potassium status is another variable which the body attempts to defend with considerable vigor Though the cells can store surplus potassium in amounts equaling between 5 and 10 per cent of their normal content (i e about 3 mEq per kg of total body weight), the organism normally eliminates such excess cellular potassium by way of the kidneys *within a few hours, thereby rendering the cells capable of buffering a potassium* load once again The adrenal cortices play an essential role in this reaction The capacity to store surplus potassium temporarily within body cells constitutes a valuable defense against dangerous degrees of hyperkalemia and gives us the ability to handle much larger loads of potassium than would be the case if we had to depend exclusively upon the renal excretory *mechanism to prevent hyperkalemia*

Hypokalemia per se does not necessarily result in maximal conservation of potassium by the kidneys On the other hand, depletion of cellular potassium stores usually does lead to conservation of this ion by the kid neys However, the body is unable to conserve cellular potassium stores when deprived of potassium unless the sodium intake also is restricted sharply *This is a fact of considerable clinical significance, for it means* that one may be causing patients to develop cellular potassium insufficiency when one maintains them on potassium free, sodium rich solutions such as isotonic saline Fortunately, this danger can be minimized by providing both sodium and potassium in physiologically tolerable amounts

* This is accomplished in large part at least by exchanging potassium ions within the cells of the renal tubules for sodium ions present *in the tubular fluid It probably ex*plains why it is necessary to take at least moderate amounts of sodium in order to excrete large amounts of potassium by way of the kidneys



17. Potassium Homeostatic System

References

Berliner (1952) General
Berliner *et al* (1950) General
Drescher *et al* (1958) Storage of surplus K+
Laragh and Stoerk (1957) Effect of serum potassium on aldesterone excretion
Spater *et al* (1959) Potassium deficiency

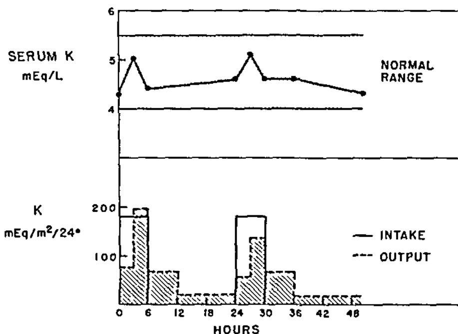
17. Potassium Homeostatic System

Though certain of the salient characteristics of this system can be discerned and described, many important details remain to be clarified It is clear that serum potassium concentration is one physiologic key variable worthy of note, for hyperkalemia per se results in various manifestations of potassium intoxication as described in the text accompanying chart 19 Moreover, it acts in some way, possibly in part via adrenocortical hormones, to stimulate excretion of potassium by the renal tubules into the urine *

Cellular potassium status is another variable which the body attempts to defend with considerable vigor Though the cells can store surplus potassium in amounts equaling between 5 and 10 per cent of their normal content (i e about 3 mEq per kg of total body weight), the organism normally eliminates such excess cellular potassium by way of the kidneys within a few hours, thereby rendering the cells capable of buffering a potassium load once again The adrenal cortices play an essential role in this reaction The capacity to store surplus potassium temporarily within body cells constitutes a valuable defense against dangerous degrees of hyperkalemia and gives us the ability to handle much larger loads of potassium than would be the case if we had to depend exclusively upon the renal excretory mechanism to prevent hyperkalemia

Hypokalemia per se does not necessarily result in maximal conservation of potassium by the kidneys On the other hand, depletion of cellular potassium stores usually does lead to conservation of this ion by the kidneys However, the body is unable to conserve cellular potassium stores when deprived of potassium unless the sodium intake also is restricted sharply This is a fact of considerable clinical significance, for it means that one may be causing patients to develop cellular potassium insufficiency when one maintains them on potassium free, sodium rich solutions such as isotonic saline Fortunately, this danger can be minimized by providing both sodium and potassium in physiologically tolerable amounts

* This is accomplished in large part at least by exchanging potassium ions within the cells of the renal tubules for sodium ions present in the tubular fluid It probably explains why it is necessary to take at least moderate amounts of sodium in order to excrete large amounts of potassium by way of the kidneys



18. Dynamics of Potassium Homeostasis

The subject of these observations was a normal adult male

18. Dynamics of Potassium Homeostasis

The data presented in the accompanying chart were obtained in the case of a healthy adult subject who was given potassium in the form of a multiple electrolyte solution A (chart 37A) at the rate of 185 mEq per m^2 per 24 hours during the first 6 hours of each day and then allowed to fast and thirst for the remainder of the 24 hour period The abrupt increase in intake from the zero level resulted in a small, transient elevation in serum potassium concentration It was followed within 6 hours by a compensatory increase in urinary output of potassium which was sufficient to restore the body's potassium content and concentration values to [illegible] control levels It is thus apparent that the nor[illegible] is capable of reacting prom[illegible] tolerance range

Reference

Neyzi *et al* (1958) Source of data for figure

doxical in view of the fact that these signs usually can be prevented by including a physiologically moderate allotment of potassium in the patient's daily intake

Symptoms and Signs of Potassium Excess and Deficit

TOO MUCH	TOO LITTLE
Hyperkalemia	Without cellular sodium excess
Elevation and peaking of T waves in ECG (lead II)	Dehydration
Muscle weakness	With cellular sodium excess
Paresthesias	Muscle weakness
Cardiac arrest	Ileus or diarrhea
	Loss of ability to concentrate urine
	Flattening of T waves in ECG (lead II)
	Hypochloremic, hypokalemic alkalosis

References

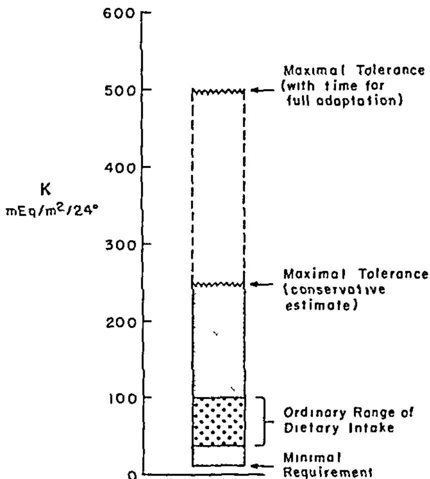
Cooke *et al* (1952) Cellular potassium lack sodium excess
Drescher *et al* (1958) Potassium intoxication in rats
Elkinton and Danowski (1955) General
Goodman and Gilman (1955) General
Spater *et al* (1959) Cellular potassium lack sodium excess
Winkler *et al* (1938) ECG changes with hyperkalemia

19. Symptoms and Signs of Potassium Excess and Deficit

Chronic loading experiments on rats indicate that the various manifestations of potassium intoxication are due to abnormally high concentrations of potassium in extracellular fluids rather than to changes in the cellular content or concentration of this ion It follows that sustained hyperkalemia *per se signifies that the organism is being subjected to a physiologically* excessive load of potassium Because hyperkalemia characteristically results in changes in the electrocardiographic T waves, under most clinical circumstances the electrocardiogram can be used in lieu of the serum potassium measurement as an index of *potassium intoxication* Digitalis tends to reduce myocardial potassium and therefore may interfere with the use of this index Acidosis also may cause changes in the T waves which can be confused with the characteristic peaking of potassium intoxication

Potassium depletion results in reduction of the potassium content of the cells In instances of simple cellular potassium deficiency, the cellular concentration remains at normal levels because there is a parallel loss of cell water Aside from producing evidences of dehydration, this type of potassium deficiency causes almost no overt manifestations If the individual is placed on a generous sodium but negligible potassium intake, sodium and small amounts of hydrogen ion are apt to enter the cells and occupy the space normally filled by potassium This sodium acts as a solute to draw water into the cell, which reduces the potassium concentration at times to markedly subnormal levels Either because of this or because of the associated fall in potassium sodium ratio, cell function deteriorates —as may be evidenced by skeletal muscle weakness, ileus, a tendency to extracellular edema formation, *loss of* capacity to concentrate urine, flattening of the T waves in lead II of the electrocardiogram, circulatory failure and other changes In addition, there is a tendency for the hydrogen ions to produce "cellular acidosis The kidneys react to this as if the patient were *suffering from metabolic acidosis* Hypochloremic, hypokalemic alkalosis results

As may be inferred from the foregoing remarks, it is sometimes difficult for the clinician to recognize potassium insufficiency unless the patient has developed cellular sodium intoxication as well This complication is often iatrogenic, arising as a consequence of maintaining patients on saline solutions or other fluids of generous sodium, but negligible potassium, content The common practice of withholding potassium from patients until they manifest some of the signs mentioned above seems para-



20. Limits of Body Tolerance for Potassium

20. Limits of Body Tolerance for Potassium

Healthy individuals can maintain equilibrium with respect to potassium while taking no more than 10 mEq per m^2 per 24 hours provided their sodium intake is low and their total caloric, carbohydrate and protein intake is large enough to maintain body protoplasm and glycogen stores

As with sodium, individuals need more time to attain maximal rates of potassium excretion than to adjust urinary output to moderate sized potassium loads In recognition of this, two maximal tolerance levels are indicated in the accompanying chart The lower one at 250 mEq per m^2 per 24 hours is a rate which normal individuals can approach or attain within several hours (chart 18) The upper value at 500 mEq per m^2 per 24 hours is one which can be reached stepwise in the course of several days Both ceiling values presuppose that the individual is taking a moderate amount of sodium salts simultaneously

As the insert shows, ordinary diets provide us with quantities of potassium which lie well within the body's safe working range of homeostatic function Among the conditions which may narrow this range, the following may be mentioned

CEILING LOWERED

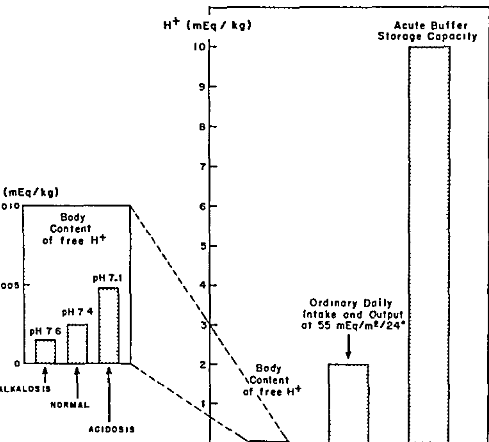
Marked dehydration
Circulatory failure
Very low sodium intake
Pannephritis with marked reduction in glomerular filtration rate (chart 45A)
Hypoadrenocorticism
Congenital adrenocortical virilism–sodium losing syndrome

FLOOR RAISED

Diarrhea
[illegible] (chart 30)
[illegible]
[illegible]

References

Shohl (1939) Normal dietary potassium
Talbot *et al* (1953) General
Talbot *et al* (1956) General



21. Body Content of Hydrogen Ions Relative to Daily Turnover

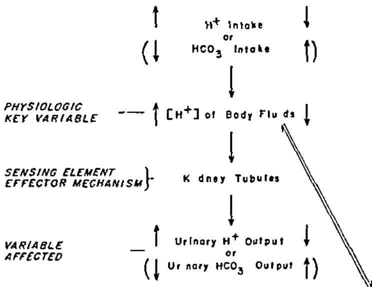
21. Body Content of Hydrogen Ions Relative to Daily Turnover

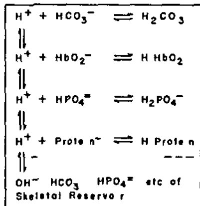
As this heading indicates, the body contains a certain amount of hydrogen ions just as it contains certain amounts of water and the various other electrolytes discussed in previous charts The absolute quantity normally present in free form in body fluids at any one moment is, however, very small, amounting to only 0 000,024 mEq per kg of total body weight when the serum pH is 7 4 *

Though the absolute quantity in body fluids is miniscule relative to ordinary daily hydrogen ion intake and output, which usually amounts to about 2 mEq per kg of body weight in a child having a surface area of 1 m^2, it constitutes a very significant "physiologic key variable " An increase in free hydrogen ion content to 0 000,048 mEq per kg results in marked acidosis (serum pH 7 1), while a decrease to 0 000,015 mEq per kg results in marked alkalosis (serum pH 7 6)

The organism is usually able to keep its free hydrogen ion content within tolerable limits despite wide variations in hydrogen ion intake because it is able to adjust output in accordance with need (chart 22) and because it contains buffers capable of temporarily absorbing up to 10 mEq of hydrogen ion per kg (chart 23)

* pH = -log hydrogen ion concentration





22 Hydrogen Ion Homeostatic System

22. Hydrogen Ion Homeostatic System

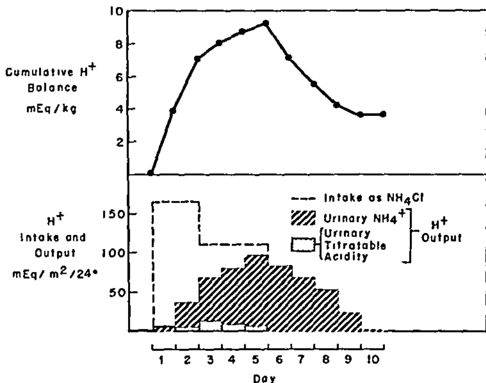
The main purpose of the accompanying diagram is to call attention to the fact that there is an intake and output of hydrogen ions just as there is of water, protein, sodium, chloride, calories and so forth Acidosis develops when the intake of hydrogen ions exceeds the output and the body content increases (serum pH $< 7\ 35$) Alkalosis ensues when the output of hydrogen ions exceeds the intake and the body content diminishes (serum pH $> 7\ 45$)

To increase the hydrogen ion content of the body, hydrogen ions must enter body fluids in company with some anion other than bicarbonate or a precursor thereof such as lactate or citrate The reason is that bicarbonate "eliminates" hydrogen ions by combining with them to form water and carbon dioxide, which is excreted by way of the lungs

Hydrogen ions presenting in company with anions such as chloride, phosphate, sulfate or mandelate constitute an intake load whether they are taken in the form of free acids or precursors such as ammonium chloride or methionine In the former instance, two molecules of ammonium ion are metabolized in the body to form one molecule of urea plus two hydrogen ions In the latter instance, the methionine molecule (which contains sulfur) upon being metabolized yields urea, hydrogen ions and sulfate ions and so forms the equivalent of sulfuric acid An abnormally large number of hydrogen ions also may be formed endogenously from lipid sources in company with two ketone anions, beta hydroxybutyrate and acetoacetate, under conditions of cellular carbohydrate starvation Unlike other forms of acidosis, this can be overcome simply by slowing the rate of ketone body formation to the point where the organism is able to metabolize the ketone acids completely to carbon dioxide and water. In nondiabetics this can be done by providing at least 50 gm of glucose per m^2 per 24 hours (chart 37B) and in diabetics by giving adequate doses of insulin (chart 40A)

Pending their elimination by the kidney tubules, all but a tiny fraction of the free hydrogen ions entering body fluids are taken up temporarily by the body's buffer systems (chart 23) The few hydrogen ions which remain free create a tendency to acidosis This serves the useful purpose of stimulating the kidney tubules to accelerate excretion of hydrogen ions in the urine (chart 24)

Hydrogen ions are made available for urinary excretion by hydration of carbon dioxide with the aid of an enzyme, carbonic anhydrase ($CO_2 + H_2O \rightarrow H^+ + HCO_3^-$) Hydrogen ions thus produced in kidney



24. Dynamics of Hydrogen Ion Homeostasis

The data for this diagram have been derived and recharted from Pitts (1948) The urinary hydrogen ion excretion from the constant diet amounting to 50 mEq per m² per 24 hours evenly divided between titrable acidity and NH_4^+, has been eliminated from the diagram The H+ output thus reflects the increase produced by the NH Cl load given on days 1 through 5 The original data did not include the subject s size We have assumed the surface area to be 1 7 m²

These data are of interest because they give an order of magnitude indication of the absolute capacity of the body as a whole to deal with abrupt loads of either of these ions pending their elimination by way of the urine As was indicated in chart 21, this capacity is generous in relation to the ordinary daily intake of hydrogen ions (about 55 mEq per m^2 or 2 mEq per kg per 24 hours or 0 7 mEq per kg per meal) It is also ample in relation to the individual dosages of sodium or potassium bicarbonate or dinarily used for alkalinization of the urine (i e about 72 mEq per m^2 or about 2 5 mEq per kg per 24 hours)

References

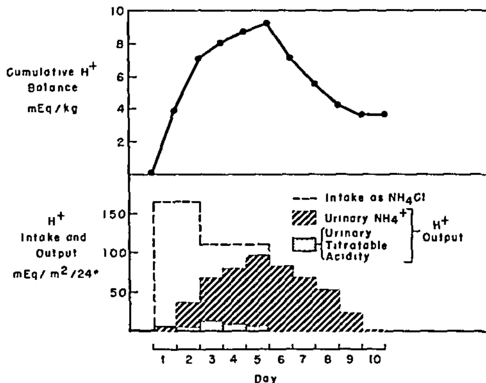
Singer *et al* (1955) Bicarbonate loading in humans
Swan and Pitts (1955) Hydrogen ion loading in nephrectomized dogs
Swan *et al* (1955) Bicarbonate loading in nephrectomized dogs

24. Dynamics of Hydrogen Ion Homeostasis

It takes about 5 days for healthy individuals to adapt to a major shift in hydrogen ion intake During the initial period of adaptation a considera ble quantity of the hydrogen ions is retained and taken up by the body's buffer systems This probably provides the stimulus needed to accelerate hydrogen ion excretion by the kidneys Only a small portion of the hydro gen ions is eliminated by the urinary buffer mechanism Most are trans ported out of the body as urinary ammonium ions

References

Pitts (1948) Source of data
Smith (1956) General



24. Dynamics of Hydrogen Ion Homeostasis

The data for this diagram have been derived and recharted from Pitts (1948). The urinary hydrogen ion excretion from the constant diet amounting to 50 mEq per m^2 per 24 hours evenly divided between titrable acidity and NH_4^+, has been eliminated from the diagram. The H^+ output thus reflects the increase produced by the NH_4Cl load given on days 1 through 5. The original data did not include the subject's size. We have assumed the surface area to be 1.7 m^2.

25. Symptoms and Signs of Hydrogen Ion Deficit and Excess

Lowering the concentration of hydrogen ions in the extracellular fluids (i e alkalosis) lessens calcium ionization and hence may lead to the development of tetany and convulsions It also can lead to *mental confusion*, coma and death It is thought that some of these manifestations may be due to spasm of cerebral blood vessels If the hydrogen ion deficit is primarily metabolic in origin, as in patients who lose hydrochloric acid through vomiting or who gain bicarbonate through overloading with substances such as sodium bicarbonate or lactate, the respirations will be decreased in number and amplitude and the concentration of bicarbonate in the serum will be elevated On the other hand, if the alkalosis is primarily a disturbance in respiratory function as in patients with hysterical hyperventilation or with hyperventilation due to salicylate intoxication, the respirations will be increased and the concentration of bicarbonate in the serum will be decreased

Acidosis is associated with a tendency to increased respiratory exchange when it is primarily due to a metabolic disorder (such as fasting ketoacidosis), but with decreased respiratory exchange when due to a respiratory disturbance which interferes with the excretion of carbon dioxide via the lungs (such as pulmonary emphysema) The concentration of bicarbonate in the serum is subnormal in the former and is supranormal in the latter type of acidosis Apart from this effect, increase in hydrogen ion concentration *per se may not produce obvious clinical manifestations* until the pH of body fluids drops to 7 1 or lower Patients with this degree of acidosis are apt to become stuporous and comatose and may die if the pH falls below 6 9 It is difficult to be sure, however, to what extent these changes should be attributed to hydrogen ion excess per se, for such individuals are usually also suffering from other disturbances such as ketosis, hyperphosphatemia, hyperchloremia, azotemia and so forth



Symptoms and Signs of Hydrogen Ion Deficit and Excess

TOO LITTLE	TOO MUCH
If metabolic alkalosis	If metabolic acidosis
Decreased respiratory exchange	Increased respiratory exchange
Plasma $HCO_3 > 27$ mEq/L	Plasma $HCO_3 < 24$ mEq/L
If respiratory alkalosis	If respiratory acidosis
Increased respiratory exchange	Decreased respiratory exchange
Plasma $HCO_3 < 24$ mEq/L	Plasma $HCO_3 > 27$ mEq/L
Tetany	Stupor
Convulsions	Coma
Mental confusion	Plasma pH < 7.35
Coma	
Plasma pH > 7.45	

References

Elkinton and Danowski (1955) General
Kety and Schmidt (1948) Cerebral blood flow in alkalosis
Moore (1958) General

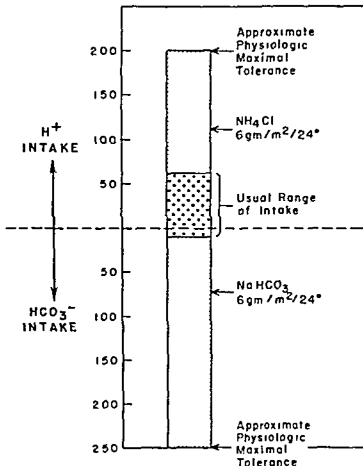
26. Limits of Tolerance for Hydrogen Ions and Bicarbonate Ions

The largest amount of hydrogen ions that can be taken and eliminated without producing a sustained acidosis is approximately 200 mEq per m^2 per 24 hours Higher rates of intake result in higher rates of output, but at the expense of systemic acidosis While the lethal limit of hydrogen tolerance is not accurately known, it would appear to be in excess of 500 mEq per m^2 per 24 hours

Alternatively, healthy individuals can take and eliminate as much as 250 mEq of bicarbonate per m^2 per 24 hours without elevating plasma bicarbonate concentration above 28 mEq per liter or becoming alkalotic By raising plasma bicarbonate concentration to higher levels, greater rates of output can be attained Though it is clear that one can take and eliminate more than 250 mEq per m^2 per 24 hours, data defining where the lethal levels of intake may lie do not appear to be available

References

Følling (1929) Hydrogen ion ceiling
Gamble (1958) Bicarbonate ceiling
Gamble *et al* (1951) Bicarbonate ceiling
Pitts *et al* (1949) Bicarbonate ceiling
Sartorius *et al* (1949) Hydrogen ion ceiling
Shohl (1939) Dietary intake of hydrogen ions



26. Limits of Tolerance for Hydrogen Ions and Bicarbonate Ions

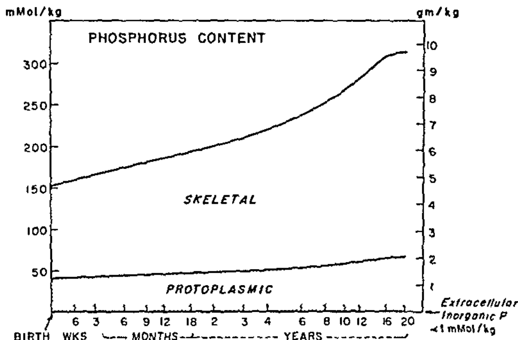
28. Body Content and Distribution of Phosphorus and Serum Inorganic Phosphorus Concentration at Various Ages

There is a gradual increase in skeletal phosphorus and hence in total phosphorus per *kilogram* of body weight during the growth period It is interesting to note that protoplasmic phosphorus comprises about 20 per cent of the body's stores Approximately half of this, or 10 per cent of total body stores, is in the form of the vitally essential, energy rich phosphate compound adenosin triphosphate (ATP), which is present in all cells, and creatine phosphate, which is found chiefly in muscles Extracellular inorganic phosphate comprises less than 1 per cent of the body's content

The concentration of inorganic phosphorus in the serum is about 5 6 mg per 100 ml at birth The values obtained during the first days of life are influenced markedly by intake, being much lower in babies fed human milk than in those fed cow's milk (chart 34) Apart from these neonatal phenomena, the inorganic phosphorus of the serum rises steadily after birth until a maximal value of about 6 5 mg per 100 ml is reached at 6 months of age It then falls somewhat, ranging between 4 0 and 5 5 mg per 100 ml in children aged 1 to 12 years and between 3 0 and 5 0 mg per 100 ml in children aged 12 to 20 years In adults it ranges between 2 5 and 5 0 mg per 100 ml

References

Elkinton and Danowski (1955) General
Gardner *et al* (1950) Neonatal phosphorus concentration
Shohl (1939) General



28. Body Content and Distribution of Phosphorus at Various Ages

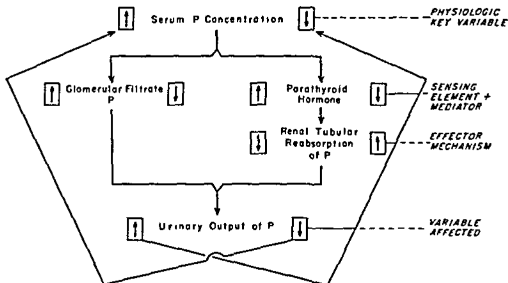
The distribution of body phosphorus at birth and in adult life has been taken from carcass analysis. The rate of increase in content was assumed to parallel the normal linear growth rate.

29. Phosphorus Homeostatic System

The accompanying diagram depicts serum inorganic phosphorus concentration as the physiologic key variable for which the phosphorus homeostatic system is responsible This undoubtedly is an oversimplification, since the parathyroids also have a responsibility for maintaining the concentration of ionized calcium in the serum within physiologically satisfactory limits Indeed, it is possible that the parathyroids sense changes in inorganic phosphorus concentration indirectly through the effects of alterations in this variable upon serum ionized calcium concentration Elevation of serum inorganic phosphorus results in a drop in ionized calcium concentration and there is no doubt that the latter change can lead to a marked increase in parathyroid secretory activity

In the absence of parathyroid hormone the renal tubules tend to reabsorb essentially all the phosphorus contained in the glomerular filtrate, with the result that the urine is almost phosphate free By contrast, when parathyroid hormone influence is at maximal levels, the tubules stop reabsorbing phosphate almost completely Consequently, the urine now contains all the phosphate of the glomerular filtrate In healthy older children and adults, who form glomerular filtrate at the rate of about 100 liters per m^2 per 24 hours and whose serum inorganic phosphorus concentration ranges from 3 5 to 5 mg per 100 ml, the glomerular filtrate will contain between 3500 and 5000 mg of phosphorus per m^2 per 24 hours Because these figures are considerably in excess of the normal dietary phosphorus content, it is possible for normal persons to vary their intake from zero to 4000 mg of phosphorus per m^2 per 24 hours without becoming excessively hypo- or hyperphosphatemic

Once this upper limit has been reached, the organism can no longer prevent accumulations of phosphorus in the circulation by suppressing renal tubule reabsorption of glomerular filtrate phosphorus Administration of larger quantities of phosphorus therefore inevitably produces hyperphosphatemia This automatically brings into prominence the other mechanism for increasing the phosphorus output rate, namely elevation of the glomerular filtrate phosphorus content (left hand section of chart 29) This mechanism is rarely needed to any great extent by normal persons, but it may be of considerable importance in patients whose glomerular filtration rate has fallen to less than 10 or 15 per cent of normal as a result of kidney disease or circulatory failure or whose parathyroid–renal tubule system is defective and therefore unable to stop reabsorbing phosphorus (charts 45, 46)



29. Phosphorus Homeostatic System

T F Nicholson has recently presented evidence which indicates that parathyroid hormone may control urinary phosphorus output by regulating renal tubule phosphorus *excretion* rather than renal tubule phosphorus reabsorption as shown in this diagram Though this may mean that the mechanism by which parathyroid hormone exerts its influence upon urinary phosphorus differs from that indicated in the present diagram it does not alter the basic concept of the role of the parathyroid glands in body phosphorus homeostasis

References

Albright and Reifenstein (1948) General
Crawford *et al* (1950) General
Nicholson (1959) Parathyroid action
Nicholson and Shepherd (1959) Renal phosphate output
Talbot *et al* (1952) General

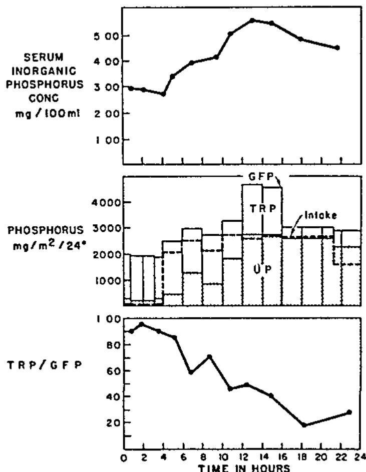
30. Dynamics of Phosphorus Homeostasis

When the phosphorus intake is increased abruptly, as it was in the normal subject of the accompanying chart, both of the mechanisms for augmenting phosphorus excretion mentioned in the preceding chart are brought into play Thus, it can be seen that raising the phosphorus intake rate from zero to about 2000 mg per m^2 per 24 hours at the fourth hour of observation resulted almost immediately in elevation of serum inorganic phosphorus concentration As indicated in the left hand section of chart 29, this led to an increase in glomerular filtrate phosphorus (GFP) and hence to a rise in urinary output of phosphorus (UP) In addition, the hyperphosphatemia stimulated the parathyroid mechanism (right-hand section of chart 29) to suppress tubular reabsorption of phosphorus (TRP), thus allowing more of the glomerular phosphorus to escape into the urine This effect is reflected in the values for TRP/GFP, which started to decline within 3 hours after the phosphorus load was imposed and reached minimal levels about 12 hours later Thus the organism was able by means of these two mechanisms to re equate output with intake within 8 hours and to return serum inorganic phosphorus concentration almost to normal levels within 18 hours after the rate of intake had been increased markedly

Studies on patients whose phosphorus intake has been suddenly reduced indicate that downward adjustments in the rate of phosphorus output also can be completed in about 12 hours

Reference

Crawford *et al* (1950) Source of data



30. Response of a Normal Subject to Phosphorus-Loading by Intravenous Infusion

The data in the above chart are from Crawford *et al* (1950)

31. Symptoms and Signs of Phosphorus Excess and Deficit

Administration of phosphorus at physiologically excessive rates results in hyperphosphatemia Though any sustained elevation of serum inorganic phosphorus concentration above normal levels may be considered evidence that the individual is being subjected to a physiologically excessive load of phosphorus, slight to moderate elevations may not lead to grossly observable disturbances in body economy With marked hyperphosphatemia, serum ionized calcium values are apt to become depressed sufficiently to result in tetany (chart 34) In other words, there is a considerable depth to the phosphorus ceiling zone, which starts at the level where the serum inorganic phosphorus concentration first rises above normal and ends at the much higher level (usually > 10 mg per 100 ml) where serious symptoms may occur

This fact has a bearing on the management of nephritic patients whose physiologic tolerance for phosphorus has been reduced to such an *extent that they can no longer eat diets of ordinary phosphorus content* without becoming moderately hyperphosphatemic Though it is essential to restrict their phosphorus intake sufficiently to prevent marked degrees of hyperphosphatemia, it may not be of vital importance to reduce their phosphorus intake *to the point where the serum inorganic phosphorus* concentration is kept within normal limits

Phosphorus deficiency is seldom accompanied by obvious clinical manifestations unless sustained for a considerable period of time It then results in hypophosphatemia, in reduction of the product of serum inorganic calcium and serum inorganic phosphorus and hence in failure to calcify the skeleton Osteomalacia (rickets) ensues Though this situation has been produced many times in laboratory animals, it is rarely encountered in clinical practice

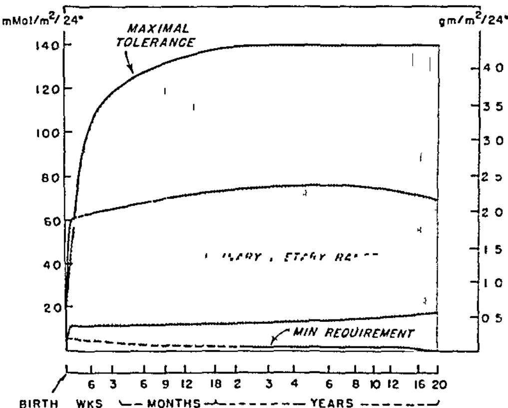
Symptoms and Signs of *Phosphorus Excess and Deficit*

TOO MUCH	TOO LITTLE
Hyperphosphatemia	Hypophosphatemia
Hypocalcemia	Osteomalacia (rickets)
Tetany	? other effects

References

32. Normal Limits of Body Tolerance for Phosphorus

As the accompanying chart shows the ceiling for phosphorus is low during the neonatal period both because the glomerular filtration rate is about half as great in newborn infants as it is in persons over 1 year of age and because the parathyroid–renal system is relatively inactive at the time of birth During the neonatal period it is important to avoid feeding infants more phosphorus than they can handle in a physiologic manner (see Cows Milk Tetany of the Newborn chart 34) Thereafter because the parathyroid–renal system rapidly acquires full functional capacity there is little likelihood that the normal individual will eat more phosphorus than he can eliminate without difficulty



32 Normal Limits of Body Tolerance for Phosphorus

Because phosphorus is a common dietary constituent, normal persons almost always ingest enough to cover their minimal requirements About the only exception that one is apt to encounter clinically is the patient with vitamin D resistant rickets In such individuals the phosphorus floor may be artificially elevated by the large doses of vitamin D needed to facilitate calcium absorption by the gut

Other conditions which may alter the range of tolerance for phosphorus are as follows

CEILING LOWERED

Normal newborn (chart 34)
Pannephritis with marked reduction in glomerular filtration rate (chart 45A)

one resistant, renal

Circulatory failure

FLOOR RAISED

Vitamin D intoxication
Hyperparathyroidism

References

Crawford *et al* (1955) *Phosphaturic effect of vitamin D*
Macy (1942) Dietary phosphorus
Rubin *et al* (1949) Renal limitations in infancy
Shohl (1939) Dietary phosphorus
Talbot *et al* (1952) Phosphorus tolerance

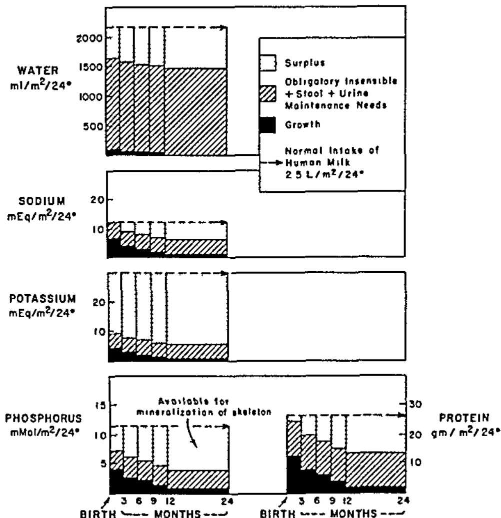
SECTION B. CLINICAL APPLICATIONS

33. Infant Feeding

Infants tend to do well on any regimen which provides essential nutrients at rates which fulfill maintenance and growth requirements, yet do not overload the capacity of any of their homeostatic systems As would be expected, human milk is so composed that the nursling infant obtains all essential nutrients at adequate yet physiologically tolerable rates when he ingests a volume that satisfies his thirst and hunger (i e about 2500 ml per m^2 per 24 hours) As charts 33A and B show, this quantity provides 1800 calories per m^2 of body surface per 24 hours and more than enough water, minerals and protein to cover growth and minimal maintenance requirements Any surpluses remaining after these primary needs have been met can easily be eliminated by way of the urine under the direction of the homeostatic systems Moreover, the infant can draw upon these surpluses, together with the quantities normally used for growth, when he needs to compensate for unusual or abnormal losses incurred as a result of sweating, diarrhea or vomiting

The situation is quite different in infants fed whole cow's milk, because it contains per unit volume and per calorie much more sodium, potassium, chloride, phosphorus, calcium and protein than its human counterpart Unlike the calf, which can use most of the absorbed materials for growth purposes, the infant must excrete all but the small fraction that can be utilized for new tissue For one thing, this produces a urinary solute load which is much greater (about 600 mosM per m^2 per 24 hours) than that found in breast-fed babies (about 200 mosM per m^2 per 24 hours) This solute load in turn increases minimal urine volume and hence total body water requirements by 400 to 600 ml per m^2 per 24 hours, thereby eliminating the margin of safety with respect to water balance enjoyed by breast-fed infants For another thing, the load of phosphorus imposed when young infants are fed undiluted cow's milk exceeds their physiologic maximal tolerance Consequently, it is apt to result in hyperphosphatemia (chart 34) It is thus apparent that whole cow's milk is not well suited to the needs or tolerances of babies during their initial weeks of life

The four right-hand columns of chart 33B are representative of the many clinical and commercial attempts to modify whole cow's milk in a manner that renders it more suitable for infant-feeding While none of these products resembles human milk exactly, all provide nutrients at rates which healthy infants should tolerate without difficulty after they are 3 weeks old During the first 3 weeks of life, when the capacity to conserve water and to eliminate phosphorus is relatively low, only formulae of low phosphate and other solute content should be used



33A. Approximate Requirements of Infants for Water, Certain Electrolytes and Protein

Technical Details

Each 100 ml of formula D contains 66 ml of whole cow's milk, 34 ml of water and a quantity of added carbohydrate sufficient to provide the calories contained in 34 ml of whole milk, namely $\frac{34 \times 0\ 7}{4}$ or 6 gm of sugar

Each 100 ml of formula E contains 50 ml of whole cow's milk, 50 ml of water and $\frac{50 \times 0\ 7}{4}$ or 9 gm of added carbohydrate

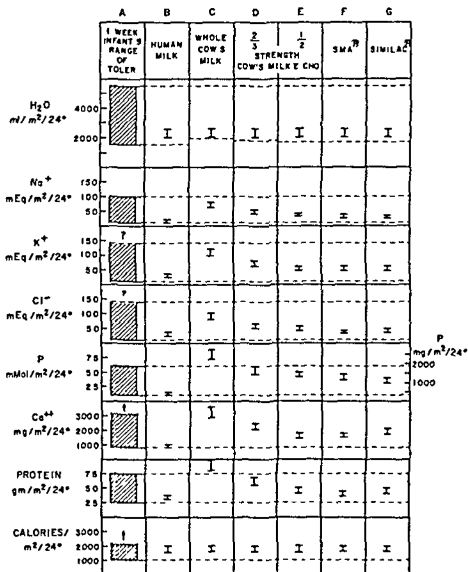
If evaporated milk is used instead of whole cow s milk, the ratio of milk to water in formula D would be EM 33 ml water 67 ml and sugar 6 gm and in formula E it would be EM 25 ml water 75 ml and sugar 9 gm

No specific volume of formula is prescribed Rather, it is suggested that the infant be *offered* 2500 ml per m^2 per 24 hours (170 ml per kg, 2½ oz per lb) in six, five or four divided allotments and be allowed to take as much as he wants in a feeding period of approximately 20 minutes' duration

By the time infants are about 2 or 3 months old, their homeostatic systems have developed to the point where it is safe to use whole cow's milk and to begin to add suitable prepared cereals, meats, eggs, fruits and vegetables as needed to give variety to the diet and to satisfy the appetite Infants given whole cow's milk should have access to plain water two or three times a day, especially in hot weather

References

Gamble (1958) General
Gardner *et al* (*1950*) *Neonatal tetany*
Nelson (1954) General
Shohl (1939) Milk composition, growth requirements



33B. Provision of Infants' Nutritional Needs by Human Milk, Whole Cow's Milk and Cow's Milk Formulae

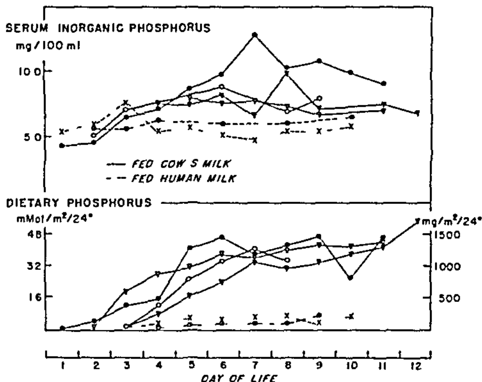
34. Cow's Milk Tetany of the Newborn

This is a condition usually seen between the fifth and twelfth days of life in infants fed whole cow's milk or other high phosphate mixtures As the accompanying chart shows, the high phosphate intake predisposes to hyperphosphatemia This lowers the concentration of ionized calcium in the serum Up to the point when the concentration of inorganic phosphorus in the serum is less than 10 mg per 100 ml, clinical signs of tetany usually are absent On the other hand, when the phosphorus concentration rises above 10 mg per 100 ml the baby usually becomes hyperirritable and jittery and may have localized twitchings or generalized convulsions

The fact that the disease occurs rarely if ever in babies fed human milk indicates it to be a product of artificial feeding It can be avoided by keeping the phosphate intake within physiologic limits of tolerance during the neonatal period Once it has developed, an immediate attempt to stop convulsions should be made by *slowly* infusing 10 or 20 ml of a 10 per cent calcium levulinate or gluconate solution Thereafter, the most important step is to eliminate phosphorus from the infant's intake for a few days, which will enable him to excrete the surplus phosphorus that has accumulated in his body and will thereby restore his serum inorganic phosphorus concentration to normal levels This can be done most easily by feeding the infant water containing 10 per cent dextrose It also can be accomplished by feeding human milk One must remember that even the most highly diluted cow's milk preparations (chart 33B) have a generous phosphorus content They should therefore be omitted until the infant has restored his serum inorganic phosphorus and ionized calcium values to normal levels Formulae containing minimal amounts of phosphorus can then be offered with safety

References

Gardner *et al* (1950) Source of diagram
Talbot *et al* (1952) General



34 Relation between Dietary Phosphorus Intake and Serum Inorganic Phosphorus Concentration during the First Days of Life

The data in the above chart are from Gardner *et al* (1950)

35. Relative Importance of Homeostatic Adjustments versus Composition of Solution Used in Recovery of Patients Undergoing Parenteral Fluid Therapy

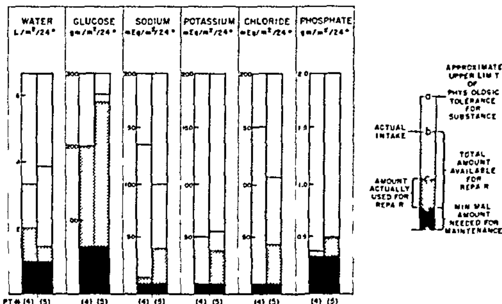
It may be helpful to introduce these discussions of parenteral fluid therapy by summarizing observations of two infants who were treated for dehydration due to diarrhea In each instance the physician in-charge had calculated the baby's maintenance plus-repair needs and treated him accordingly In each instance, also, measurements were made which permitted one to judge in retrospect how the patient had responded to therapy.

The results obtained were thought provoking, for they showed that *though we had miscalculated these infants' needs by an appreciable margin* and had given the largest allotments of various substances to the infant who needed them the least and the smallest to the infant who needed them the most, yet both had done well It then became apparent that the patients had recovered satisfactorily because, by good fortune, both had been given water, sugar, sodium, potassium, chloride and phosphate at adequate, yet physiologically tolerable, rates Consequently, it was possible for the infants to cure themselves by retaining or rejecting each of the ingested substances *in accordance with needs as they sensed them*

This experience made one realize that the physician does not necessarily have to know exactly what his patient's specific maintenance and repair requirements are It is necessary only that he make a reasonably good estimate of his patient's homeostatic capabilities and provide him with raw materials at rates which fall within them Factors to be considered in the application of this homeostatic principle to the practice of parenteral fluid therapy will be considered with the aid of the charts that follow

Reference

Talbot *et al* (1955) Source of diagram



35. Relation between Intake and Retention by Two Infants Recovering from Dehydration Due to Severe Diarrhea

The data in the above chart are from Talbot *et al* (1955)

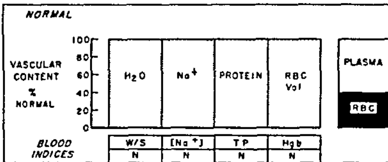
36. Correction of Hypovolemia

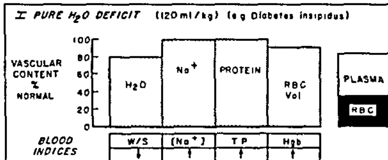
Because circulatory insufficiency can result in marked functional impairment of the body's homeostatic systems, it is of prime importance to consider the cardiovascular status of each patient at the onset of parenteral fluid therapy Whenever a patient shows such signs of circulatory insufficiency as hypotension, weak thready pulse, cold clammy extremities or cyanotic mottling of the skin, the possibility that these changes are due to hypovolemia should be suspected

As the accompanying charts indicate, blood volume may become markedly reduced by deficits in whole blood, plasma, extracellular fluid or total body water Because these fluids have different volumes of distribution and comprise different fractions of total body mass, they vary considerably with respect to the absolute deficits needed to reduce blood volume to a given extent *An approximately valid picture of these relations* may be had by assuming that vascular volume shrinks in direct proportion to the loss of its main constituents from the body as a whole Thus the loss of either 120 ml of water alone, 83 ml of extracellular fluid, 17 ml of plasma or 16 ml of whole blood per kg of body weight would reduce the blood volume by approximately 20 per cent

When water is lost, but solutes, plasma and red blood cells are retained, the serum water solute ratio is subnormal, the serum sodium and *protein concentrations are high and the hemoglobin is elevated (section* I of chart 36) This is the type of situation which one may encounter in patients with diabetes insipidus When there is a loss of sodium and its companion anions in physiologic proportion to water, as may occur in patients suffering from diarrhea, vomiting, marked sweating or adrenocortical insufficiency, the serum water solute ratio and sodium concentration remain normal, but the total protein and hemoglobin concentrations rise [illegible] there has not been a proportional loss of erythrocytes (section III of chart 36)

It will be remembered that hypovolemia produces a tendency to expand extracellular fluid volume (chart 11) When this occurs, residual circulating albumin becomes diluted and hypoproteinemia results These same phenomena may be observed in patients whose blood volume has become reduced by hemorrhage (*section IV of chart 36*)



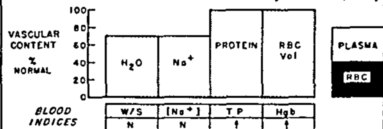


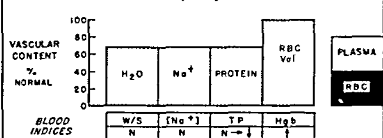
36. Theoretical Types of Hypovolemia

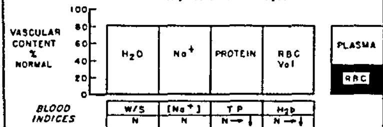
Calculations of the different types of deficits necessary to produce a 20 per cent loss of blood volume were based on the following values for normal total body content water—60 per cent of body weight extracellular volume—25 per cent of body weight, blood volume—8 per cent of body weight plasma volume—5 per cent of body weight

Generally speaking, it is not necessary or even desirable, to restore vascular volume to normal in a few minutes It is important, however, to increase blood volume promptly to a point where circulatory efficiency is regained (chart 14) In most instances this can be accomplished by the intravenous administration in two hours of a quantity of fluid equal to about a third of the deficits indicated in the various sections of this chart Unless plain water is clearly indicated (section I of chart 36), in which case 40 ml of 5 per cent dextrose in water would be appropriate, a dose of 25 ml of saline, 6 ml of plasma and/or 6 ml of whole blood per kg would be safer and more effective

If such doses of saline, plasma or whole blood fail to restore circulatory efficiency, it is probable that the difficulty is due to cardiac or vascular failure rather than to hypovolemia Accordingly, unless there has been a rapid and continuing loss of extracellular fluid, serum or blood, such patients are not likely to benefit from the administration of additional doses of these fluids They are more apt to respond favorably to vasopressor agents such as levarterenol or aramine bitartrate







36. Theoretical Types of Hypovolemia: Cont'd

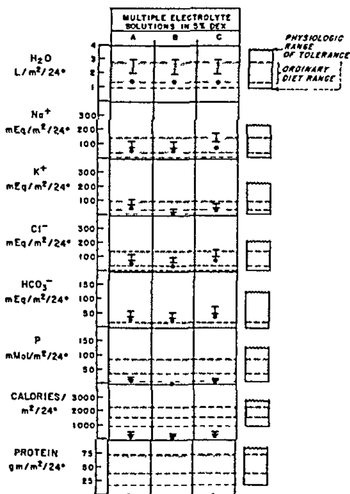
37. *Solutions* for Total Body Repair plus Maintenance Therapy

The three solutions shown in chart 37A are representative of many now available which can be used *to provide glucose and extracellular and intracellular electrolytes* in physiologically tolerable proportions As the black circles show, when these solutions are administered at a rate of about 1300 ml per m^2 of body surface per 24 hours, which covers the minimal maintenance need for water, they supply the organism with at least minimal maintenance allotments of the various other constituents Likewise, as the vertical bars indicate, one can safely provide the additional water and electrolytes which may be required to cover abnormal maintenance needs by increasing the intake rates of these solutions up to 3000 ml per m^2 per 24 hours

All these fluids are hypertonic when administered, since they contain from 300 to 600 mosM of glucose and from 100 to 180 mosM of electrolytes per liter, but they become hypotonic in relation to body fluids when the glucose contained in them is metabolized within the body This is desirable because it means that only one quarter or at most only one half of the water infused will be needed to cover the electrolytes during their stay in the body (at 3 6 ml per mosM) or during their elimination from the body in the urine (at 0 7 to 1 5 ml per mosM) (charts 4, 8) The remainder of the water is therefore available to compensate for insensible water losses and to eliminate endogenous waste products via the kidneys

Patients undergoing parenteral fluid therapy are apt to need potassium as much as they need sodium (chart 40) Despite this and the fact that body tolerance for potassium under most circumstances greatly exceeds the doses used, most parenteral fluids contain much less potassium than sodium Of the fluids shown here, solution A contains approximately equal amounts of these two ions (*K 35* mEq, *Na 40 mEq per liter*) *while* solution B has less than one third as much potassium as sodium (K 12 mEq Na 40 mEq per liter) and solution C about half as much potassium as sodium (*K 25 mEq, Na 60 mEq per liter*)

Because maintenance and repair needs for chloride may parallel and even exceed those for sodium (chart 39), it has seemed appropriate to use this as *the chief anion of parenteral fluid solutions* Under many and perhaps most circumstances, it might be as well not to dilute the chloride with bicarbonate (or lactate) or phosphate Though commonly included, [illegible] ntake than its bio- [illegible] North American or European diet The quantities of bicarbonate (or lactate)



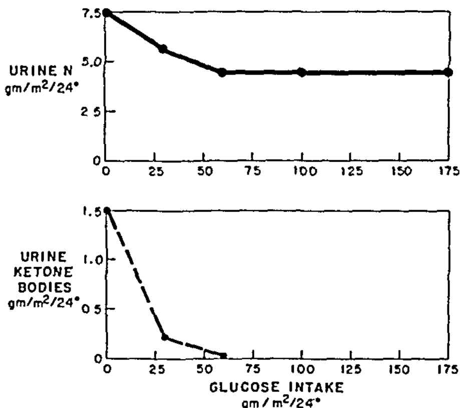
37A. Multiple Electrolyte Solutions for Parenteral Fluid Therapy

	Na	K	Mg	Cl	Lact	HPO_4
Solution A	40	35	–	40	20	15
Solution B	40	12	–	35	17	
Solution C	60	25	5	53	25	12

The electrolyte concentrations are expressed in mEq/L. See references for sources.

provided by the present solutions should, however, be well tolerated because they do not pose an excessive load on the body's hydrogen ion–bicarbonate ion homeostatic system Likewise, though the phosphate may not be necessary, it provides the depleted organism with readily available phosphate, which it can use either for glycogen formation, cellular fluid repair or urinary buffer purposes

Even when given at minimal maintenance rates, fluids containing 50 or more gm of glucose per liter deliver more than the 50 gm of sugar needed per m^2 per 24 hours to prevent ketosis and to reduce protoplasmic catabolism to minimal levels (chart 37B) Such fluids do not, however, fulfill the body's total caloric requirements This is not important to well-nourished patients, who will be able to resume oral feedings within a week or 10 days On the other hand, it may be of vital importance to patients who are severely depleted or who must be nourished parenterally for longer periods of time (chart 37C) Under these circumstances, it may be desirable to fortify the multiple electrolyte solution with calories in the form of additional glucose (up to 250 gm per m^2 per 24 hours), fat, alcohol and/or amino acids Though fat preparations have not been entirely satisfactory, they may be worth considering in cases of marked caloric deficit Amino acids are well tolerated and can be given as 2 5 or 5 gm/100 ml solution They may also be of value in providing the organism with material from which protein can be formed Available data indicate, however, that the body is apt to use amino acids largely as a source of energy unless its caloric needs are being provided for by adequate allotments of carbohydrate and fat (chart 37D) In view of the difficulties inherent in making it possible for debilitated patients to synthesize protein, it sometimes is important to administer preformed protein as plasma or crystalline albumin and/or erythrocytes in the form of a whole blood transfusion These are strongly indicated in patients who, because of hypovolemia, are manifesting circulatory insufficiency (chart 36), water intoxication (chart 42A) or edema (chart 44C) Such signs are apt to occur only after prolonged or very severe illnesses in older children and adults However, they can appear in infants within a few days after the onset of a major infection or nutritional upset



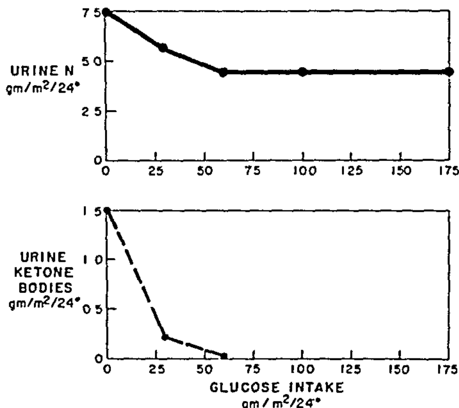
37B. Amount of Glucose Needed to Suppress Ketonuria and Reduce Urine Nitrogen Output to Minimal Levels

References

Butler *et al* (1945) Source of data, chart 37B
Flett *et al* (1949) Solution B (1 part Darrow s solution, 2 parts 5 per cent D/W), chart 37A
Lowe (1955) Solution C, chart 37A
Shohl (1939) General, chart 37C
Talbot *et al* (1952) Source of diagram chart 37D
Talbot *et al* (1953) Solution A, chart 37A
Talbot and Richie (1958) Source of d agram, chart 37C

provided by the present solutions should, however, be well tolerated because they do not pose an excessive load on the body's hydrogen ion–bicarbonate ion homeostatic system Likewise, though the phosphate may not be necessary, it provides the depleted organism with readily available phosphate, which it can use either for glycogen formation, cellular fluid repair or urinary buffer purposes

Even when given at minimal maintenance rates, fluids containing 50 or more gm of glucose per liter deliver more than the 50 gm of sugar needed per m^2 per 24 hours to prevent ketosis and to reduce protoplasmic catabolism to minimal levels (chart 37B) Such fluids do not, however, fulfill the body's total caloric requirements This is not important to well-nourished patients, who will be able to resume oral feedings within a week or 10 days On the other hand, it may be of vital importance to patients who are severely depleted or who must be nourished parenterally for longer periods of time (chart 37C) Under these circumstances, it may be desirable to fortify the multiple electrolyte solution with calories in the form of additional glucose (up to 250 gm per m^2 per 24 hours), fat, alcohol and/or amino acids Though fat preparations have not been entirely satisfactory, they may be worth considering in cases of marked caloric deficit Amino acids are well tolerated and can be given as 2 5 or 5 gm/100 ml solution They may also be of value in providing the organism with material from which protein can be formed Available data indicate, however, that the body is apt to use amino acids largely as a source of energy unless its caloric needs are being provided for by adequate allotments of carbohydrate and fat (chart 37D) In view of the difficulties inherent in making it possible for debilitated patients to synthesize protein, it some times is important to administer preformed protein as plasma or crystalline albumin and/or erythrocytes in the form of a whole blood transfusion These are strongly indicated in patients who, because of hypovolemia, are manifesting circulatory insufficiency (chart 36), water intoxication (chart 42A) or edema (chart 44C) Such signs are apt to occur only after pro longed or very severe illnesses in older children and adults However, they can appear in infants within a few days after the onset of a major infection or nutritional upset



37B Amount of Glucose Needed to Suppress Ketonuria and Reduce Urine Nitrogen Output to Minimal Levels

References

Butler *et al* (1945) Source of data chart 37B

Flett *et al* (1949) Solut on B (1 part Darrow s solut on 2 parts 5 per cent D/W) chart 37A

Lowe (1955) Solut on C chart 37A

Shohl (1939) General chart 37C

Talbot et al (1952) Source of d agram chart 37D

Talbot *et al* (1953) Solut n A chart 37A

Talbot and Rich e (1955) Source of d agram chart 37C

38. Maintenance Therapy with Multiple Electrolyte Solution

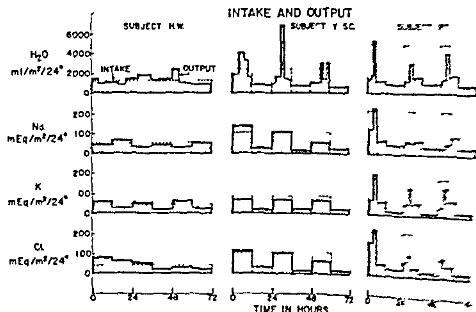
The data recorded in the accompanying charts were obtained from pairs of healthy adults who were maintained on a total of 1500 ml of multiple electrolyte solution A (chart 37A) per m per 24 hours for a total of 3 days As chart 38A shows one pair of subjects received their allotments steadily at a rate of 125 ml per m per hour throughout the 24 hour period of observation (left hand division) The second pair of subjects received their allotments in the first 12 hours of each day* (middle division) while the third pair of subjects received their allotments in the first 6 hours of each day (right hand division) All individuals were then fasted and thirsted for the remainder of each 24 hour interval

Those on the 24 hour regimen were able to keep body water and electrolyte content and concentration values close to normal control levels with a minimum of homeostatic effort On the other hand the 12 hour and particularly the 6 hour subjects had to make wide adjustments in rate of output to prevent body content and concentration values from fluctuating to an important extent This is documented in chart 38B where it can be seen that the individuals on the 24 hour regimen utilized less than 20 per cent of adult capacity to excrete water sodium potassium chloride and phosphate by way of the urine By contrast those on the 12 hour and especially those on the 6 hour regimen varied their rates of output from the physiologic minimal to almost the physiologic maximal level Had the subjects been infants instead of adults the loads imposed by the 12 and 6 hour regimens would have over reached homeostatic capacities

The effects of over reaching homeostatic capacities can be visualized by comparing the solid with the interrupted lines of chart 38C The former represent the changes in body content which actually occurred The latter indicate the changes which would have occurred in 12 and 6 hour subjects during each infusion period if concomitant adjustments in rate of output had failed to take place Those on the 12 hour regimen would have augmented their body water and electrolyte stores by 1 to 3 5 per cent and those on the 6 hour schedule by 3 to 5 per cent by the end of the intake periods One cannot abruptly increase the body s total water or potassium by much more than 5 per cent without intoxicating the subject

These observations show that it is physiologically safest to spread the daily maintenance allotment evenly over the 24 hours This form of ther

* To compensate for the reduction in time the rate of administration was increased to 250 ml per m² per hour in the 12 hour subjects and to 500 ml per m per hour in the 6 hour subjects



38 A Maintenance by Multiple Electrolyte Solution

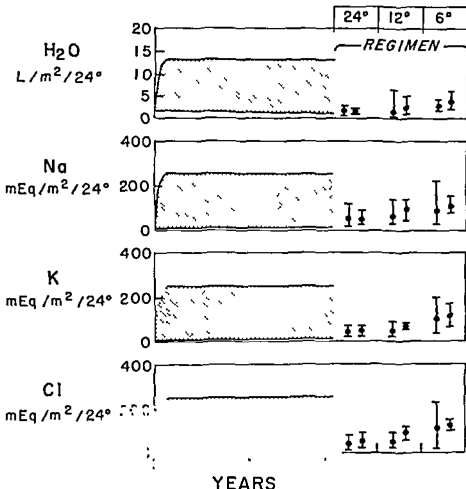
T

apy imposes so little strain on the body s stabilizing mechanism that it should be well tolerated by all except those suffering from ... ment of homeostatic function Moreover it results in ... of body water and electrolyte stores and practically el... cies to weakness headache nausea hunger and thirst ... given their day s allotment in 12 or 6 hours and then ... for 12 or 18 hours.

Continuous infusions can be carried out in the care ... and adults without difficulty by means of ordinary sets ... bulb delivers 1 ml per 15 to 20 drops In dealing w... infants it is preferable to use a set containing a drip ... about 1 ml per 60 drops

References

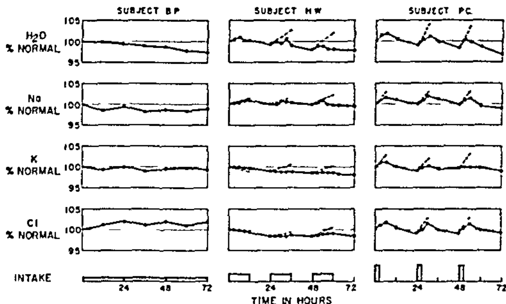
Neyzi et al (1958) Source of data and diagrams charts ...
Sh...(1957) Intravenous infusion set f... infants



38B. Maintenance by Multiple Electrolyte Solution: Cont'd

Relations between rates of output observed for subjects on various regimens (right-hand section) and physiologic ranges of excretory capacity (left hand section) The ... and the vertical bars traversing them the

al (1958)



38C. Effects of the 24-, 12- and 6-Hour Regimens on Body Content Values

These measurements were made on subjects similar to those represented in charts 38A and B. The solid lines in this diagram represent data derived from balance measurements. The interrupted lines represent the gains (or losses) that would have occurred during the periods of administration if no homeostatic adjustments in rate of output had occurred during these periods; where the lines are absent, data concerning output rates immediately before the infusion period are lacking. From Nevzi *et al.* (1958).

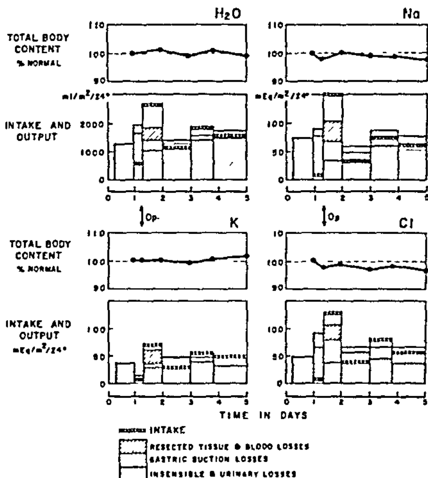
39. Maintenance of Patients Subjected to Major Gastrointestinal Surgery

It has become customary in many clinics to maintain patients undergoing surgery *with dextrose in water or dextrose in saline solutions* Though these forms of maintenance may be innocuous if used advisedly and for a short time only they do impose a considerable and at times excessive burden upon the homeostatic systems Thus most individuals given electrolyte free dextrose in water must reduce their rates of electrolyte output from ordinary dietary levels to essentially zero within a short time if they are to escape serious depletion of the extracellular and intracellular solute stores Moreover they are likely to develop water intoxication unless the dosage of this electrolyte free solution is carefully controlled (chart 42A)

Those given approximately isotonic saline solutions are not apt to develop water intoxication but they must eliminate the sodium contained in them with high efficiency if they are to avoid developing the cellular *potassium insufficiency–sodium intoxication syndrome* (chart 19) As others have shown this is a difficult accomplishment for persons undergoing the stress of anesthesia and surgery since stress acting via the adrenocortical system produces strong tendencies to sodium accumulation and to cellular potassium depletion

The accompanying chart sets forth data which indicate that this problem may be avoided by giving surgical patients ordinary allotments of both potassium and sodium together with the main intracellular and extracellular anions The subject of this diagram was one of a series of five adult patients who were followed closely during the hours preceding and the days following an extensive subtotal gastrectomy for control of peptic ulcer A nasogastric tube was inserted and all food and fluids by mouth were stopped approximately 16 hours preoperatively Anesthesia was induced with thiopental (pentothal) and the surgery performed with the patient under ether anesthesia The operation lasted about 5 hours

About 200 ml of saline 700 ml of 5 per cent dextrose in water and 1000 ml of whole blood were given intravenously during the operative period Thereafter the patient was given by vein 1200 ml of multiple electrolyte solution A (chart 37A) per m^2 per 24 hours as a basal maintenance allotment To this was added an amount equal to the volume of fluid currently being lost by way of the nasogastric tube In the present case this initially amounted to about 500 ml per m^2 per 24 hours and then gradually diminished



39. Maintenance of a Patient Subjected to Gastrointestinal Surgery

These data are from studies by Border, Talbot, Lincoln and Terry (to be published).

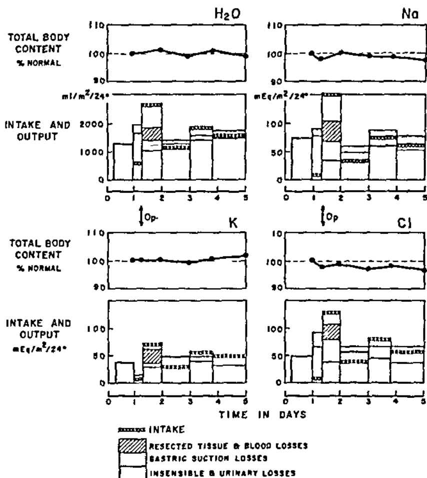
39. Maintenance of Patients Subjected to Major Gastrointestinal Surgery

It has become customary in many clinics to maintain patients undergoing surgery with dextrose in water or dextrose in saline solutions Though these forms of maintenance may be innocuous if used advisedly and for a short time only they do impose a considerable and at times excessive burden upon the homeostatic systems Thus most individuals given electrolyte free dextrose in water must reduce their rates of electrolyte output from ordinary dietary levels to essentially zero within a short time if they are to escape serious depletion of the extracellular and intracellular solute stores Moreover they are likely to develop water intoxication unless the dosage of this electrolyte free solution is carefully controlled (chart 42A)

Those given approximately isotonic saline solutions are not apt to develop water intoxication but they must eliminate the sodium contained in them with high efficiency if they are to avoid developing the cellular potassium insufficiency–sodium intoxication syndrome (chart 19) As others have shown this is a difficult accomplishment for persons undergoing the stress of anesthesia and surgery since stress acting via the adrenocortical system produces strong tendencies to sodium accumulation and to cellular potassium depletion

The accompanying chart sets forth data which indicate that this problem may be avoided by giving surgical patients ordinary allotments of both potassium and sodium together with the main intracellular and extracellular anions The subject of this diagram was one of a series of five adult patients who were followed closely during the hours preceding and the days following an extensive subtotal gastrectomy for control of peptic ulcer A nasogastric tube was inserted and all food and fluids by mouth were stopped approximately 16 hours preoperatively Anesthesia was induced with thiopental (pentothal) and the surgery performed with the patient under ether anesthesia The operation lasted about 5 hours

About 200 ml of saline 700 ml of 5 per cent dextrose in water and 1000 ml of whole blood were given intravenously during the operative period Thereafter the patient was given by vein 1200 ml of multiple electrolyte solution A (chart 37A) per m^2 per 24 hours as a basal maintenance allotment To this was added an amount equal to the volume of fluid currently being lost by way of the nasogastric tube In the present case this initially amounted to about 500 ml per m per 24 hours and then gradually diminished



39. Maintenance of a Patient Subjected to Gastrointestinal Surgery

These data are from studies by Border, Talbot, Lincoln and Terry (to be published)

By the end of the fifth day the patient was able to resume oral feedings It can be seen that he kept his body water, sodium, potassium and chloride content values close to the normal starting levels Though they are not recorded here, he maintained extracellular and intracellular electrolyte concentration values equally close to normal control levels He did so by making such adjustments in urinary output as were needed to maintain equilibrium

The results obtained in this case are reasonably representative of those found for four of the five individuals studied In the case of the fifth patient, gastric suction losses amounted to more than 500 ml per m^2 per 24 hours during the first postoperative days The chloride contained in these gastric fluids exceeded that being provided by the multiple electro lyte solution (about 70 mEq per m^2 per 24 hours) by a small margin Consequently, though the patient reduced his extragastric losses of chloride to zero, he was unable to maintain his body chloride stores at normal levels This trend was reversed by an added intake of 50 mEq of sodium chloride per m^2 per 24 hours

From these experiences it may be concluded that patients can maintain metabolic normalcy with considerable efficiency even while undergoing the homeostatic stresses of anesthesia major surgery and postoperative gastrointestinal drainage if they are provided with water and the chief extracellular and intracellular electrolytes in reasonable amounts The multiple electrolyte solution used here appears adequate for patients losing up to 500 ml of gastrointestinal fluid per m^2 per 24 hours For those losing more than this amount, it would seem advisable to cover losses in excess of 500 ml per m^2 per 24 hours with isotonic saline

References

Border *et al* (to be published) Source of data

Moore (1958) Postoperative sodium and water retention

Moore and Ball (1952) Postoperative sodium and water retention grading surgical stress

40. Treatment of Diabetic Ketoacidosis

The subject of the accompanying charts was a 15-year-old girl who presented with diabetic ketoacidosis of 3 days' duration When first seen she was markedly dehydrated and had the rapid, deep respirations characteristic of severe ketosis The urine was found to have high sugar and ketone-body content An electrocardiogram did not reveal any changes in the T waves suggestive of potassium intoxication Serum chemical measurements showed her to be moderately hyperglycemic (blood sugar 420 mg per 100 ml), very acidotic (serum pH 6 9, serum bicarbonate 5 mEq per liter) and markedly hypohydrated (serum water-solute ratio 3 0 ml per mosM) In spite of all this, her pulse was strong and her blood pressure satisfactory Accordingly, it appeared unnecessary to expand vascular volume prior to intravenous infusion of a multiple electrolyte solution which contained potassium

Shortly after admission, therefore, she was given 150 units of crystalline insulin * At the same time an intravenous infusion of multiple electrolyte solution A (chart 37A) was started and given at a rate of 4000 ml per m^2 per 24 hours Initially, this solution was made up in water without dextrose Two hours later, when the blood sugar had fallen to 200 mg per 100 ml, a multiple electrolyte solution containing dextrose (5 gm/100 ml) was substituted for the sugar-free solution At the end of 6½ hours the rate of infusion was reduced to 2900 ml per m^2 per 24 hours The patient was able to take sips of water by mouth by the fifteenth hour, and it became possible to feed her entirely by mouth by the eighteenth hour From the second day, her intake was maintained at previous levels by giving her measured quantities of food and fluids of known composition

It can be seen in the right-hand diagrams (chart 40A) that the blood sugar fell and that serum pH and bicarbonate values commenced to rise shortly after this therapy was instituted, reaching normal levels in less than 20 hours Serum pH values overshot normal levels slightly during the period of equilibration Serum bicarbonate values approached normal levels in a smooth, steady manner These changes in acid base balance were due in part to the provision of base bicarbonate in the form of sodium and potassium lactate, they were due mainly to the fact that ketone acids disappeared as the administered insulin made it possible for cells to use carbohydrate instead of fat as a source of energy

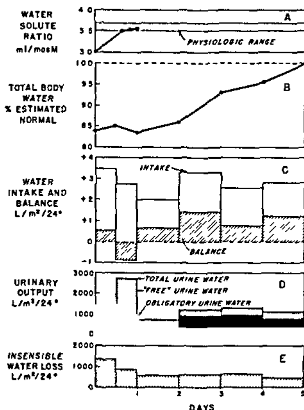
* She had been given 30 units each of protamine zinc and crystalline insulin 6 hours prior to admission It was on this account that no long acting insulin was given at the time of entry

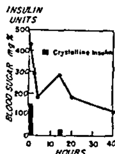
The left-hand diagram of chart 40A shows that the ratio of water to solutes in body fluids also rose promptly to the physiologic range This rise was due in part to the 500 ml gain in total body water indicated in sections B and C and in part to the reduction of approximately 800 mosM in body solutes which occurred as the hyperglycemia and ketosis were overcome Insofar as the water-solute ratio was concerned, this reduction in solutes was equivalent to the addition of about 2 5 liters of solute free water to the intake during the first half day of therapy During the same period, when there was a deficit of water relative to solutes in the body fluids, the patient passed urine of minimal water content Thereafter, in close accordance with rapidly changing needs, she began to dilute her urine with the surplus water which became available as repair needs and insensible losses diminished

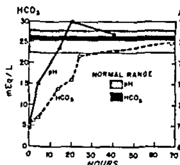
Chart 40B shows that the patient conserved sodium until she had re tained a quantity equal to about 9 per cent of the normal content of the body This was the amount needed to restore the extracellular sodium content *and concentration to normal Thereafter she eliminated sodium as* fast as she received it Potassium was stored in relatively larger quantities and for a longer period of time This too appeared to be governed by need, for calculations indicated that the patient still had an intracellular potassium deficit at the close of the 5 day observation period Despite the fact that she had lost almost 20 per cent of her potassium stores, she never was hypokalemic Almost all the phosphorus offered was retained There was, however, no retention of chloride ions This appeared appropriate, since the serum chloride concentration was normal and there was nothing to suggest extracellular fluid volume insufficiency

These observations are representative of many recorded in the literature which demonstrate that patients with diabetic ketoacidosis have a very real capacity to overcome their various metabolic disturbances when provided with insulin and reasonable allotments of water and electrolytes They accomplish this by retaining and rejecting water and extracellular and intracellular ions in close accordance with rapidly changing requirements In other words, the organism reacts according to its specific needs The fact that it can do so largely eliminates the necessity to obtain an extensive series of chemical measurements of serum and urine constituents This is fortunate because it may take several days even for a well equipped team to determine exactly the specific status and hence the maintenance and repair requirements of a given individual at a given moment

In practice, it usually suffices to certify the diagnosis by demonstrating that the patient is hyperglycemic and ketonemic or ketonuric In this







40A. Insulin and Multiple Electrolyte Therapy

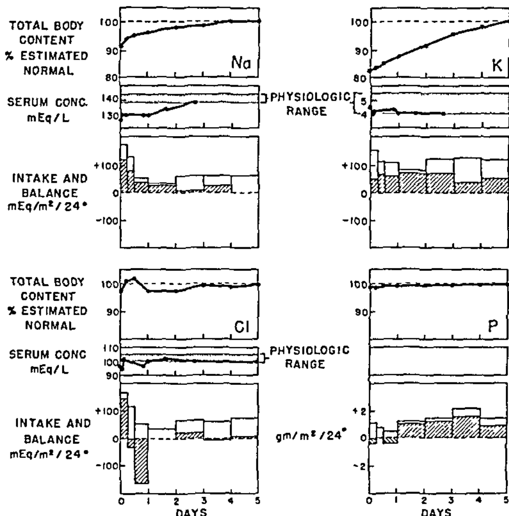
The above chart shows the effects of insulin and multiple electrolyte solution therapy upon the body water (left section) blood sugar (right upper), serum pH and bicarbonate (right lower) status of a patient with severe diabetic ketoacidosis The patient weighed 51 kg and had an estimated body surface of 1 5 m² From Talbot *et al* (1955)

clinic, it is customary to treat these manifestations of insulin lack by giving, for each square meter of body surface, 75 units of crystalline insulin intravenously plus 75 units subcutaneously as an initial dose At the same time, the anticipated daily maintenance dose of a long acting insulin such as protamine zinc (i e about 20 units per m^2) is given subcutaneously Thereafter crystalline insulin doses are repeated at intervals of 2 to 4 hours, as indicated by urine and/or blood sugar determinations, until normal values are attained

If the patient appears to be suffering from circulatory collapse, he is given by vein a vascular volume expansion dose of sugar free saline within the first 90 to 120 minutes * If he is not suffering from circulatory insufficiency and there are no signs of potassium intoxication (chart 19), a multiple electrolyte solution (chart 37A) is given intravenously at the rate of 2500 to 3500 ml per m per 24 hours until such time as he can take this solution or its equivalent by mouth The lower rate should suffice for patients who are only mildly acidotic and dehydrated, even in severely depleted and acidotic patients, it rarely is necessary to exceed the higher rate The patient is shifted to ordinary foods and fluids by mouth as he can tolerate them

* The recommended dose is 25 ml per kg (chart 36) However initiation of therapy with sugar free electrolyte solution may be considered a nonessential refinement

References



40B. Insulin and Multiple Electrolyte Therapy: Cont'd

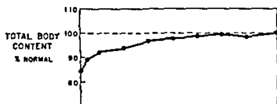
The above chart shows the effects of insulin and multiple electrolyte solution therapy upon the body electrolyte status of the diabetic patient of chart 40A. From Talbot *et al* (1955)

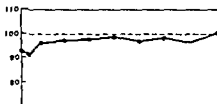
41. Therapy of a Diarrheal Infant

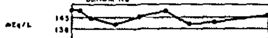
The patient of this chart was a 1-month old infant weighing 3 8 kg who became depleted and dehydrated as a result of severe diarrhea of several days' duration In contrast to the diabetic girl of chart 40A, he showed signs of circulatory insufficiency when first seen Accordingly, his therapy consisted initially in the administration of saline in dextrose at the rate of 2300 ml per m^2 per day for the first 6 hours By the end of that time, his circulatory status was considered to be satisfactory and he was started on multiple electrolyte solution A of chart 37A at the rate of 3000 ml per m^2 per 24 hours, a rate closely similar to that used for the diabetic patient of chart 40A Balance measurements showed, however, that the infant used the nutrients thus provided in a quite different manner This was most strikingly evident with regard to sodium and potassium Whereas the diabetic girl retained much more potassium than sodium, the diarrheal infant retained more of the latter than the former ion Both adjusted their balances in a smooth, asymptotic manner, well suited to their specific maintenance plus repair needs and both did well clinically

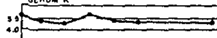
Reference

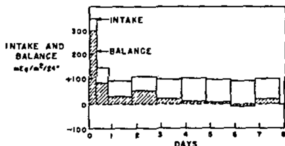
Talbot et al (1955) General

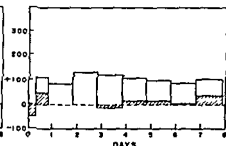












41. Selective Retention of Sodium and Potassium by an Infant Recovering from Dehydration Due to Diarrhea

The subject of this chart was a 1-month-old male infant weighing 3.8 kg and having a surface area of about 0.2 m^2

42. The Water Intoxication Problem

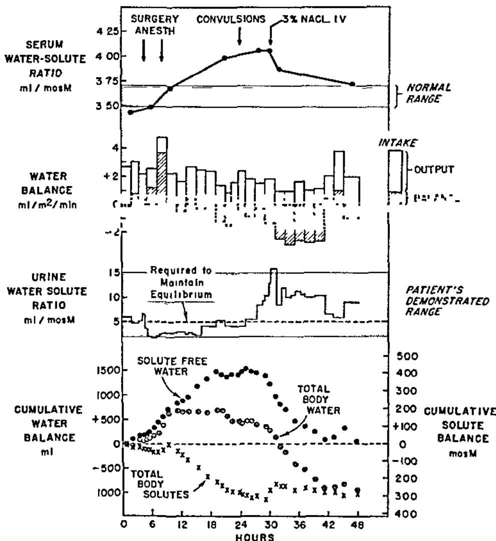
The subject of chart 42A is representative of many patients in whom water intoxication has developed accidentally while they were being maintained on parenteral fluids following general anesthesia and surgery

In this case, an intravenous infusion of solution A (chart 37A) was started a few hours before surgery at a rate approximating 2400 ml per m² per 24 hours During the preoperative period the patient had no difficulty in maintaining water and electrolyte homeostasis The picture changed, however, when he was subjected to ether anesthesia and surgical exploration of his craniopharyngioma The urine water solute ratio then fell abruptly from the 5 ml per mosM level required to maintain equilibrium to levels characteristic of maximal antidiuretic hormone activity Between the fifth and tenth hours this produced an increase in body water relative to body solutes At about the tenth hour, the patient stopped gaining water and started to lose solutes This led to further elevation of body water solute ratio values, here represented by the serum measurements

Unfortunately, these trends were not suspected clinically until the patient commenced to have generalized convulsions 14 hours postoperatively When emergency studies carried out at that time revealed that these convulsions were probably due to water intoxication, the patient was given by vein 4 ml of 0 5 molar (3 per cent) solution of sodium chloride per kg of body weight His response was prompt and favorable He had commenced to dilute his urine shortly before this treatment was given, and from then onwards he had no more difficulties

It is now known that many general anesthetic agents and morphine type drugs, as well as injury to the blood brain barrier in the region of the hypothalamus can result in uncontrolled release of antidiuretic hormone and hence can predispose to the events recorded above It also is known that water loading by expansion of the vascular volume can cause an extracellular solute diuresis of the sort observed between the tenth and twenty ninth hours in the present instance

These difficulties can be avoided by giving only a minimal maintenance allotment of water to patients who are undergoing general anesthesia receiving repeated doses of narcotics or suffering from encephalitis, meningitis or severe brain trauma If electrolyte free dextrose in water solutions are used, the rate should approximate 1200 to 1300 ml per m² per 24 hours For half isotonic solutions such as solution A of chart 37A, from 1300 to 1500 ml per m² per 24 hours would be suitable Though the



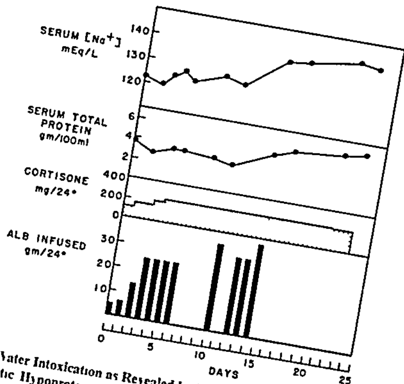
42A. Water Intoxication Following Partial Surgical Removal of a Craniopharyngioma

The subject of the above chart was a 14 year-old boy From Crawford and Dodge (1959)

danger of water intoxication can be avoided entirely by using isotonic saline, one is apt to produce sodium intoxication if one gives enough of this solution to cover insensible and urinary losses of water

The therapy used for the control of this patient's convulsions was based on the following assumptions and calculations First, it is known that the body contains normally about 600 ml of water and 170 mosM of solute per kg of body weight It follows that in order to lower the water solute ratio of body fluids by 0 1 ml per mosM the patient must either lose approximately 17 ml of water or gain about 6 mosM of solute per kg of body weight While there are times when it is reasonable simply to discontinue fluid intake and allow a water intoxicated patient to cure himself by eliminating surplus water when serious manifestations such as convulsions are present it is preferable to correct the disturbance promptly by administering solutes This can be accomplished by administering intravenously, for each kilogram of body weight approximately 6 ml either of 0 5 molar (3 per cent) saline solution or of 1 0 molar (18 per cent) mannitol solution both of which contain 1 mosM of solute per ml Unless the patient s sodium stores are depleted it is preferable to use mannitol and thereby avoid sodium intoxication Hypertonic saline is indicated however, when there are signs of sodium depletion (charts 13, 36) The initial dose, which is designed to reduce the ratio of water to solutes in body fluids about 0 1 ml per mosM often suffices Should it fail to control the manifestations of water intoxication the dose can be repeated once

Elevation of the serum water solute ratio and hyponatremia may be observed also in patients suffering from left heart failure or from hypovolemia due to lack of red blood cells plasma proteins or extracellular electrolytes This is illustrated by the nephrotic child of chart 42B, who was found to have serum water solute ratio values of approximately 4 0 ml per mosM and serum sodium concentration values approximating 120 mEq per liter He was at this time grossly edematous and was exhibiting signs indicative of circulatory insufficiency (weakness rapid thin pulse, pallor, cold extremities, mottling of the skin) Inasmuch as he had no evidences of cardiac disease it was concluded that these signs of circulatory insufficiency were due to hypovolemia It was further presumed that the hypovolemia was caused by hypoproteinemia (total serum protein 2 gm per 100 ml) rather than by lack of red blood cells (blood hemoglobin 17 gm per 100 ml) or of extracellular electrolytes (edema fluid +++) Accordingly, he was given a series of albumin infusions together with cortisone in doses sufficient to control his albuminuria Perhaps because he reached this elevated water solute ratio gradually he did not show clear-



Water Intoxication as Revealed by Hyponatremia in a Patient with Nephrotic Hypoproteinemia

The subject of the above chart was a 5 year-old boy with an average weight of 28 kg

cut clinical manifestations of water intoxication though a disturbing tremulousness may have represented warning symptoms

The signs of circulatory insufficiency disappeared shortly after the first plasma infusion was started Later as serum protein stores were replenished serum sodium concentration values which were used here as an inverse index of body water solute relationships also returned to normal The patient was losing water and sodium (i e edema fluid) as the serum sodium concentration was rising Thus the rise in sodium concentration was due to the shedding of water in excess of sodium rather than to an absolute gain in body sodium content

This phenomenon is easily explained if one accepts the thesis that the neurohypophyseal system is designed basically for the purpose of sustaining circulation at effective levels (charts 4 44B) For the system to

fulfill this purpose by maintaining the ratio of water to solutes in bod fluids within the range of 3 5 to 3 7 ml per mosM, it is essential that bod stores of red blood cells, plasma protein and extracellular electrolytes b at least at minimally satisfactory levels and that the person be capable of an adequate cardiac output A deficiency in any of these ancillary factors results in a chronic tendency to circulatory insufficiency and hence in a continuous stimulus to the neurohypophyseal system to conserve and store water relative to solutes Among other things, this induces a tendency to hyponatremia When this is due to extracellular solute deficiency (e g in patients who have lost large amounts of sodium as a result of sweating or hypoadrenocorticism), sodium chloride administration constitutes appropriate treatment On the other hand, hyponatremia consequent to hypoproteinemia and/or anemia are best treated by administering plasma or whole blood or by taking such other steps as appear indicated to raise the oncotic pressure of the blood to satisfactory levels Likewise, hyponatremia due to cardiac failure will disappear spontaneously if cardiac output can be restored by means of digitalis and other standard remedies

Additional information concerning the etiology and management of water intoxication will be found in the sections which deal with pannephritis (charts 45A–C)

References

Crawford and Dodge (1959) General and source of diagram chart 42A
Leaf *et al* (1953) Solute diuresis caused by water retention
Talbot *et al* (1957) General chart 42B

43. Parenteral Fluid Therapy for Burned Patients

Physicians may find the following description of the guides to therapy currently being used by this service of help in deciding about the management of severely burned patients. These remarks will be concerned only with steps aimed (a) at sustaining vascular volume by replacing blood constituents lost as a result of the burn in accordance with need (chart 36) and (b) at providing maintenance allotments of water and sugar (charts 37A, 38A). They cover the first 48 hours. By that time most patients are ready for an ordinary maintenance regimen.

In considering vascular replacement needs, it is helpful to estimate the area of the burn in square meters. This can be done by first determining the patient's total surface area in square meters from body weight measurement (graphs A and B, see inside front cover). The proportion of this area which has been damaged can then be estimated with the aid of chart 43.

Generally speaking, it is advisable to institute parenteral fluid therapy in all patients who have had more than 5 per cent of their skin burned. An indwelling urethral catheter is inserted in most cases because it enables one to record urine flow at hourly intervals in a dependable manner. The airway is kept clear, with artificial aids if necessary, both to assure oxygenation and to prevent the occurrence of respiratory acidosis secondary to inadequate ventilation. Morphine, demerol and similar narcotics are avoided if possible because they predispose to water intoxication (chart 42A).

Patients are apt to need *for each square meter of area burned* approximately 4000 ml of plasma during the first 8 hours after the injury, 4000 ml during the next 16 hours and 4000 ml during the ensuing 24 hours. Accordingly, an intravenous infusion designed to deliver plasma* at the indicated rate is started promptly. At the same time, a separate intravenous infusion of 5 per cent dextrose in water is initiated at the rate of 1500 ml *per m² of total body surface per 24 hours*.

Blood pressure, urine flow, urine specific gravity, blood hemoglobin, total serum protein and if possible serum water-solute ratio measurements are made every hour for the first several hours and thereafter as often as necessary to keep aware of the patient's needs. Arrows are used to indicate that changes in value may be of importance as well as absolute levels.

* If the urine and serum are visibly discolored with hemoglobin and/or the patient is found to have a low hematocrit reading, it is recommended that whole blood instead of plasma be used initially.

Ordinary normal standards of reference may be used with respect to blood pressure and blood and serum concentration measurements There are no single ideal values for urine flow or urine specific gravity Roughly speaking, it is desirable to maintain urine flow above 40 ml per m" per *hour* since this may constitute the least amount needed to eliminate the large mass of waste products created by the burn injury It also may be ad vantageous to keep the specific gravity below 1 025, since this should re duce the likelihood of tubular cast formation

Though these measurements are intended as an aid to physicians in estimating the status of the patient's blood volume, none give direct information concerning this vitally important variable It follows therefore that one must deduce from clinical observations and such measurements as these whether the patient is hypovolemic, euvolemic or hypervolemic Since individuals are apt to show alterations in blood pressure which correlate quite closely with alterations in blood volume, serial measurements of this index are helpful It must also be remembered that both hypovolemia and simple water deficit tend to reduce the flow and increase the specific gravity of urine (chart 44D) Hypervolemia and simple water excess tend to produce opposite changes

Once it has been ascertained that a patient has hypo- or hypervolemia, the nature of the deficit or excess responsible for this abnormality can be told with considerable dependability by blood hemoglobin, serum protein and serum water-solute measurements (chart 36) The resultant information can then be used as a basis for deciding whether the patient needs more or less dextrose in water, plasma or whole blood

After 48 hours have passed, it usually is possible to initiate ordinary feedings and to give plasma or blood intermittently as indicated

Bedside Guides for Modifying Burn Therapy

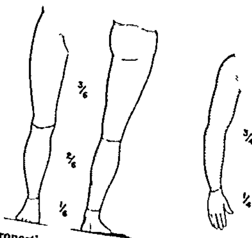
	Blood pressure	Urine flow	Urine sp gr	Blood hgb	Serum protein	Serum ml/mosM	Change indicated
A	N	↓	↑	↑	↑	↓	Speed up D/W infusion
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

References

Cope *et al* (1948) Magnitude of plasma losses in burns

Lund and Browder (1944) Body surface area proportions at various ages

	NEWBORN	3 YEARS	6 YEARS	12 + YEARS
HEAD	18 %	15 %	12 %	6 %
TRUNK	40 %	40 %	40 %	38 %
ARMS	16 %	16 %	16 %	18 %
LEGS	26 %	29 %	32 %	38 %



43. The Relative Proportions of the Major Areas of Body Surface at Various Ages

The percentage figures in the above chart refer to front and back. For example, if an individual suffered a burn of the whole anterior chest, this would comprise 10 per cent of his body surface

44. Nephrosis

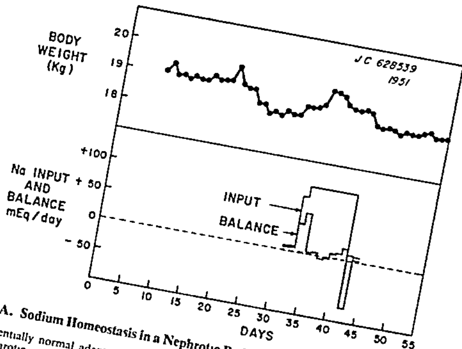
Chart 44A shows the manner in which a mildly edematous nephrotic child adapted to an abrupt increase in sodium intake. Except for a slight delay, her response was essentially the same as that observed in the healthy subject of chart 12. The same was true with respect to water homeostasis.

Taken together, these observations show that this girl's edema was the result of facultative adjustments in salt and water balance rather than the product of an absolute inability to excrete sodium and its companion anions or water. Indeed, if she had lost as much sodium during the period of low intake as on the fifth day of sodium loading she would have drained sodium from her body at the rate of 200 mEq per m^2 per 24 hours and shed edema fluid at the rate of 700 ml per m^2 per 24 hours.

Patients with nephrosis do not always remain in such a homeostatically balanced condition. As chart 44B demonstrates, there are times when they tend to retain all the sodium ingested and to use it to form ever increasing quantities of edema fluid. These trends can be reversed by repeated infusions of plasma protein supplemented by corticosteroid therapy in dosages sufficient to suppress albuminuria (chart 44C).

The etiologic and therapeutic implications of these findings may be summarized with the aid of chart 44D. The initial step in the pathogenesis of nephrotic edema is an antigen antibody reaction involving the glomerular basement membrane, which becomes attenuated and discontinuous. This results in leakage of albumin into the urine. Rates of loss in excess of 5 gm per m^2 per 24 hours produce a tendency to hypoalbuminemia. The resultant loss of oncotic materials leads to diminished vascular volume. This in turn stimulates the sodium homeostatic system to conserve sodium (chart 11). As sodium and its companion extracellular anionic solutes accumulate, they prompt the water homeostatic system to retain a physiologically equivalent amount of water (chart 4). Hypovolemia also acts directly to promote water retention, thereby creating the tendency to hyponatremia shown in chart 42B. Because there is a deficiency of oncotic material in the plasma, much of this newly formed extracellular fluid escapes into the interstitial spaces, where it accumulates as edema and ascites. If the quantity retained in the vascular tree is sufficient to restore blood volume to satisfactory levels, equilibrium is re established (chart 44B). If not, water and salt retention continues (see days 13 to 17, chart 44B).

It would thus appear that edema is the product of a series of physiologic reactions designed to counteract the tendency to hypovolemia, which

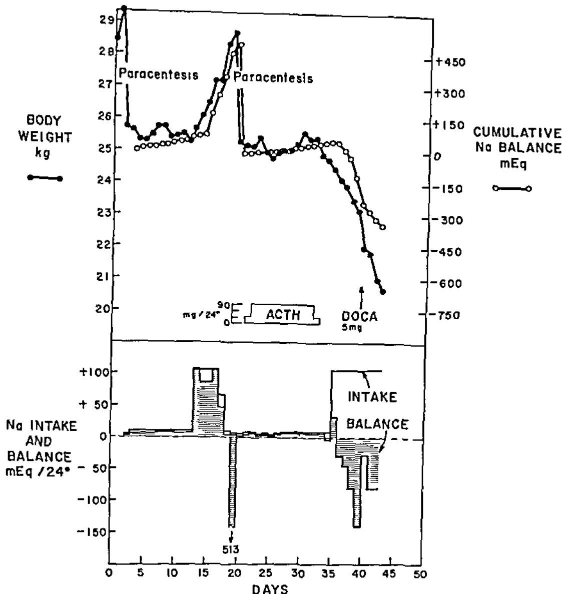


44A. Sodium Homeostasis in a Nephrotic Patient

Essentially normal adaptation to increase and to decrease in sodium intake by a nephrotic girl aged 7 years In these studies body weight was used as an index of changes in extracellular fluid volume and thus of body sodium content From Talbot *et al* (1957)

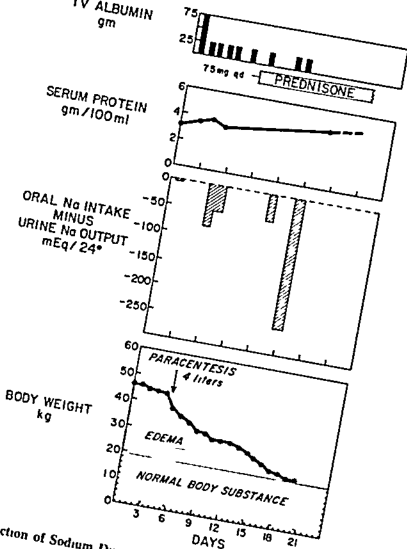
develops when large amounts of albumin are lost from the plasma It may therefore be considered "normal" for the abnormal circumstances

These observations provide a useful framework for considering the level of action of various forms of therapy As indicated at the right in chart 44D, corticosteroids exert their influence by facilitating the healing of the pathologic process responsible for albuminuria Consequently, it allows the organism to replenish its albumin stores As they become replenished, the edema is shed by normal homeostatic processes In most patients this type of diuresis can be initiated within 21 days by giving orally from 150 to 200 mg of cortisone or its equivalent per m² per 24 hours in three divided doses at 8 hour intervals This diuresis is considered a fortunate by-product of the cortisone therapy, the chief aim of which is to suppress the pathologic process in the kidneys There is substantial evidence that relapses are less frequent if cortisone is continued for a period



44B. Sodium Retention and Diuresis after ACTH Therapy

that the sodium diuresis which occurred during these days was not influenced by a major increase in sodium intake but was slowed for 1 day following the administration of a single dose of desoxycorticosterone acetate From Talbot *et al* (1957).



44C. Induction of Sodium Diuresis by Intravenous Administration of Albumin

Negative sodium balance and loss of edema fluid following repeated intravenous infusions of albumin in the nephrotic girl of chart 44A. It became unnecessary to administer albumin intravenously for the purpose of sustaining vascular volume after the albuminuria had been brought under control by prednisone therapy. From Talbot *et al* (1957)

of weeks or months after the edema has subsided until such indices of nephrotic activity as urinary albumin output, serum cholesterol concentration and the serum protein level have returned to normal

Albumin (plasma) infusions and blood transfusions constitute physiologically appropriate emergency measures to overcome extreme degrees of hypovolemia and edema (chart 44C) However, they usually are effective only temporarily up to the time when albuminuria has been suppressed by corticosteroids

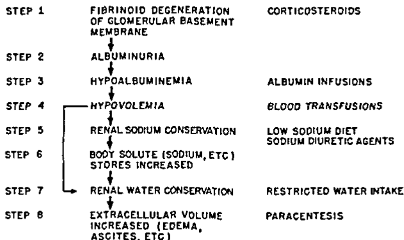
One can slow the rate of edema formation in nephrotic patients by reducing the sodium intake to minimal maintenance levels—i e about 10 mEq per m^2 per 24 hours (chart 15) On the other hand, it is practically impossible to reduce body sodium or edema by restricting the sodium intake when sodium conservation forces are acting maximally There is no need to restrict the sodium intake below ordinary dietary levels after the plasma protein has been restored to satisfactory levels by corticosteroid treatment (see days 35 to 45, chart 44B) Indeed, patients may derive considerable benefit from liberalization of the sodium intake if it results in improved appetite and hence in more positive caloric and nitrogen balances

Though patients do tend to retain water out of proportion to solutes, they rarely take enough water by mouth spontaneously to cause convulsions or other overt manifestations of water intoxication Hence, for the reasons mentioned above in connection with sodium, it rarely is necessary or desirable to impose restrictions on the water intake of nephrotic patients

Of all the procedures listed, paracentesis is the least physiologic, for it removes some of the fluid which the body has accumulated for the purpose of sustaining the circulation Paracentesis may therefore result in circulatory failure unless steps are taken to maintain vascular volume with plasma or whole blood It is now used only for the relief of serious mechanical difficulties due to gross fluid accumulation

References

Riley *et al* (1959) Cortisone therapy
Spiro (1959) Renal pathology
Talbot *et al* (1957) Pathologic physiology and source of data charts 44A–C



44D. Outline of the Pathogenesis of Nephrotic Edema, with the Levels of Action of Various Therapeutic Maneuvers

45. Pannephritis

The patient of the accompanying chart was a young man with chronic nephritis of serious proportions as evidenced by the fact that he was at various times hyperhydrated, hypohydrated, edematous, hyperkalemic, hypokalemic, acidotic, hyperchloremic, hyperphosphatemic and azotemic with a glomerular filtration rate less than 10 per cent of normal In an effort to find out how these disturbances might best be overcome, a survey was made of his ranges of tolerance for water and certain other dietary constituents In accordance with the principles set forth in chart 6, the survey was based on simultaneous consideration (a) of rates of urinary output and (b) of his metabolic status * These measurements were made promptly after admission so as not to waste opportunities to locate limits of tolerance provided by the fact that the patient had over reached a number of his "ceilings' and "floors" spontaneously

Individual data expressed in terms of intake are presented in chart 45A The ranges of tolerance indicated by these individual measurements are represented by the right hand column of each pair shown in chart 45B

Comparison of the columns representing the patient with the adjacent columns indicating normal tolerance and ordinary dietary ranges gives a fair idea of the practical problems faced by this individual His ranges of tolerance were narrowed to a degree where he could not eat and drink ad libitum in an ordinary manner without developing metabolic disturbances, but it was not so narrowed that it would be practically impossible for him to attain and maintain metabolic normalcy by taking food

* The urinary excretion rate measurements usually were made on carefully timed collections of at least 6 hours duration The oral intake equivalents of these urinary output values were calculated on the basis of the following extrarenal loss rates per m² per 24 hours water 1000 ml sodium potassium hydrogen bicarbonate and chloride ions zero phosphorus 10 mMol protein zero The following were used as indices of status for water serum ml per mosM (chart 7) for sodium evidences of extracellular fluid lack (i e dehydration) or excess (i e edema) (chart 13) for potassium serum potassium concentration and the T waves of lead II electrocardiographic tracings (chart 19) for hydrogen ion serum pH and bicarbonate concentration (chart 25) for chloride serum chloride concentration (chart 27) for phosphorus serum inorganic phosphorus concentration (chart 31) for protein blood NPN concentration In the case of phosphorus the maximal tolerance was estimated from measurement of his glomerular filtration rate by assuming maximal urinary output to be equal to glomerular filtration rate (assumed to be equal to creatinine clearance) times maximal allowable serum inorganic phosphorus concentration here arbitrarily set at 5 mg per 100 ml (chart 31) The same principle was used in estimating his maximal protein tolerance on the assumption that his urinary output would be equal to his urea clearance rate times an arbitrarily selected maximal allowable blood urea nitrogen (or NPN) concentration of 100 mg per 100 ml

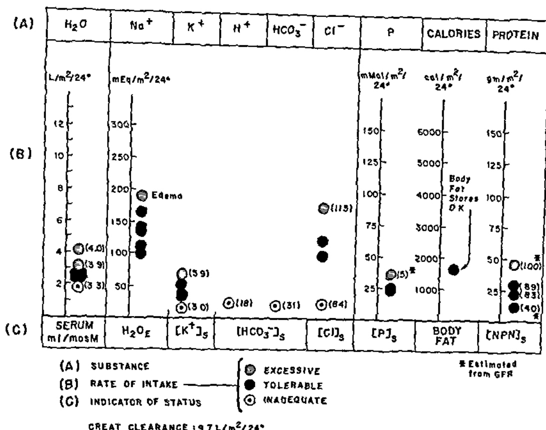
and fluid at rates which fell within his residual ranges of homeostatic tolerance.

Experience with the present and similarly handicapped patients has shown that this usually can be accomplished without too much difficulty while the individual is living in a hospital where his intake can be controlled by trained personnel. It is a different matter, however, when the patient is living at home where he and his family must play a major role in the management of the disease. Under these circumstances, one may find that dietary and other recommendations are ignored in whole or in part because the patient is unaware of their importance, or lacks the motivation to live effectively as a person, or finds the restrictions so irksome or impractical that he is more inclined to suffer the disabilities of the disease than he is to cope with the discomforts inherent in his therapy. It follows that patients with this type of enduring handicap need help from their physicians not only with respect to the management of the metabolic disorder, but also with regard to striking the best possible balance between that which may be good for the disease and that which is best for the person who has the disease.

In fulfilling this larger responsibility, in certain cases one may come closer to controlling the disease itself by granting liberties compatible with survival and passably effective living than by attempting to impose the regimen most ideally suited to control of somatic disturbances.

For instance, though one would prefer to see serum inorganic phosphorus concentration values within normal limits, it does not appear that mild degrees of hyperphosphatemia are necessarily very harmful. Accordingly, if one can keep the phosphorus intake within residual physiologic limits of tolerance only by giving distressingly large doses of aluminum hydroxide gel or by feeding a diet which is so unpalatable that the patient fails to eat enough to satisfy his caloric needs, it may be better to liberalize the diet at least to the point where body weight measurements indicate that he is in caloric balance.

Dietary protein also may deserve consideration both with regard to phosphorus, nitrogen, potassium, sulfate, hydrogen ion and total solute-loading and with regard to its influence upon the palatability of the diet. When a diet is so unpalatable that the patient eats little and is in negative caloric balance, he is apt to stop anabolizing protein and may start consuming his own body stores as a source of energy. Since positive caloric balance predisposes to protein anabolism (chart 37D), liberalization of protein intake to the point where the appetite for calories is stimulated paradoxically may result in lowering instead of raising blood NPN values.

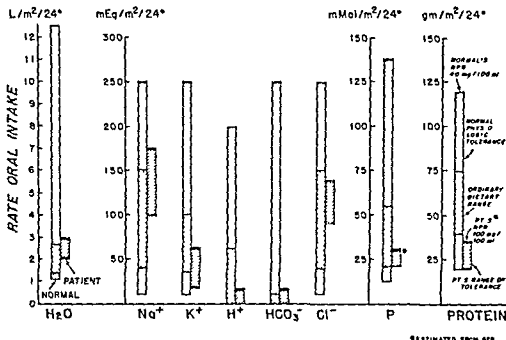


45A. Tolerance of a Pannephritic Patient for Water and Certain Other Nutrients

Each of the circles in the top division *represents a measurement of rate of intake of* the substance named in section (A) at a time when the patient's status had been assessed per the indicator of status named in section (C) If the indicator of status revealed the patient to be within normal limits, it was concluded that the corresponding rate of intake was physiologically tolerable Under this circumstance a solid black circle was used On the other hand, if the indicator of status showed that the patient had a surplus of the substance in his body, the corresponding rate of intake was considered to be physiologically excessive for that individual at that time Under this circumstance a horizontally shaded circle was used to represent the rate of intake Finally, if the indicator of status showed that the patient was deficient with regard to the substance, the intake was considered to be inadequate and a circle containing a solid dot was used The actual value of the "status indicator" is shown in the adjacent parenthesis

ever, when he took water at the rate of 4 liters per m² per 24 hours, his serum water-

continued on opposite page



45B. Tolerance of a Pannephritic Patient for Water and Certain Other Nutrients

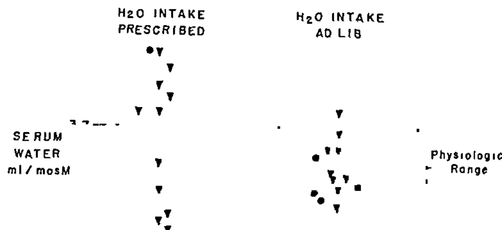
The left-hand column of each pair shows the normal limits of tolerance for certain nutrients and the ordinary dietary range. The right hand column of each pair shows the tolerance of the pannephritic patient of chart 45A. The columns representing the patient are bounded at top and bottom by solid black bars if the ceiling and/or floor is localized by the data of chart 45A; they are serrated if these data show only that the patient could raise or lower his intake to the indicated level without becoming intoxicated or depleted.

---

solute ratio was abnormally high at 4.0 ml per mosM. Contrariwise, the fact that his serum water-solute ratio was subnormal at 3.3 ml per mosM when he was taking water at the rate of 1.8 liters per m² per 24 hours indicated that this rate was physiologically inadequate.

The other abbreviations used in section (C) have the following meaning: H_2O_e = extracellular fluid volume, $[K^+]_s$ = serum potassium concentration in mEq per liter; $[HCO_3]_s$ = serum bicarbonate concentration in mEq per liter; $[Cl]_s$ = serum chloride concentration in mEq per liter; $[P]_s$ = serum inorganic phosphorus concentration in mg per 100 ml; $[NPN]_s$ = serum non protein nitrogen concentration in mg per 100 ml.

The body surface of this 22-year-old male patient was estimated to be 1.6 m².



45C. Body Water-Solute Ratio Status of Two Nephritic Patients

The left hand data were obtained during periods when their water intake was being prescribed by physicians who lacked exact knowledge about the patients limits of tolerance The right hand data were obtained when they were allowed to take water in accordance with thirst The shaded zone indicates the normal range From Kerrigan *et al* (1955)

Of the variables under consideration potassium is probably the one most likely to produce a fatal degree of intoxication Consequently, it appears essential in patients with very low tolerance for this electrolyte to emphasize the dangers of potassium excess and to give specific direction as to how to avoid it It has been noted empirically that most nephritic patients can excrete up to 1 5 times their glomerular filtrate content of potassium without becoming seriously hyperkalemic Thus a patient with a glomerular filtration rate of 5 liters per m² per 24 hours and a serum potassium concentration of 4 mEq per liter would have a glomerular filtrate potassium of 5 x 4, or 20 mEq, and an estimated tolerance for this ion of 20 x 1 5, or 30 mEq per m² per 24 hours This can be expressed to the patient in meaningful terms by making him aware of the potassium content of common foods

In these connections, it has been found that thirst may constitute a

down" with water since the volume taken in this manner may by itself overload the individual s residual homeostatic capabilities and lead to

water intoxication It also is important that patients with a low ceiling of tolerance for water should eat a relatively dry diet and then satisfy their thirst with plain water or sweetened, electrolyte free fluids rather than with milk, soup or other solutions of high fixed solute content

References

Talbot *et al* (1956) General
Kerrigan *et al* (1955) Water homeostasis and source of data chart 45C

46. Pseudohypoparathyroidism

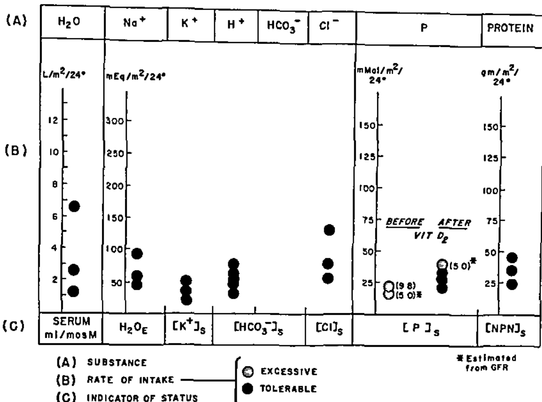
The patient of this chart presented at the clinic during infancy with laryngospasm and other manifestations of tetany The concentration of calcium in his serum was found to be markedly depressed and that of inorganic phosphorus to be markedly elevated The elevation in phosphorus concentration could be traced to a failure on the part of his kidneys to shed surplus phosphorus in the normal manner in accordance with homeostatic requirements Indeed, as this chart shows his ceiling of tolerance for phosphorus was so low that he could not take even a minimum of the ordinary dietary allotment of this substance without becoming hyperphosphatemic However, in contrast to the pannephritic patient of chart 45A he appeared not to have any other important limitations in renal function

Though his specific disturbance could not be overcome by the administration of parathyroid hormone * it could be alleviated by oral administration of 100,000 to 400 000 units of vitamin D, daily These doses raised his maximal tolerance for phosphorus to levels which were compatible with an ordinary phosphorus intake It is not known whether this therapy also raised the level of his physiologic minimal requirement for phosphorus, a possibility which would be interesting to explore

* The administration of 50 units of potent parathyroid extract per m causes a sharp and distinct increase in phosphorus clearance in hypoparathyroid or normal individuals but not in patients with nephrogenic hypoparathyroidism This is an interesting distinction but one that has little bearing on therapy for both types of hypoparathyroidism are treated similarly

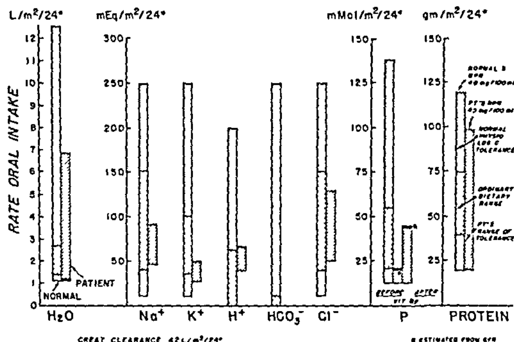
References

Albright *et al* (1942) General
Talbot *et al* (1952) General



46A. Tolerance of a Patient with Pseudohypoparathyroidism for Various Nutrients

The body surface area of this 22-year old patient was estimated to be 1 43 m². The design of the chart corresponds to that of chart 45A



46B. Tolerance of a Patient with Pseudohypoparathyroidism for Various Nutrients as Defined by Data of Chart 46A

Note the increase in the patient's tolerance for phosphorus after vitamin D_2 therapy had been started. The design of the chart corresponds to that of chart 45B

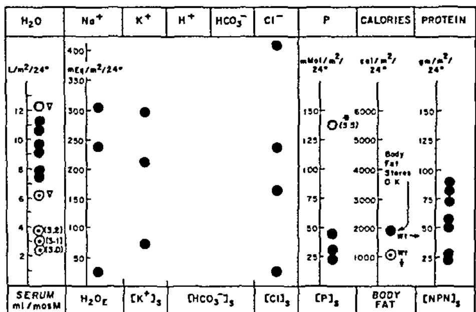
47. Nephrogenic Diabetes Insipidus of Pitressin-resistant Type

This patient tended to become severely hypohydrated, as evidenced by loss of weight and skin elasticity, dryness of the mucous membranes, hemoconcentration, lowering of the serum water-solute ratio and hypernatremia unless he was allowed to take large quantities of solute free water This disturbance was due to the fact that his kidneys were unrespon sive to antidiuretic hormone * As a consequence of this, he needed a minimum of about 15 ml of water to eliminate 1 mosM of solute from the body by way of the kidneys This meant that when he was taking whole cow's milk, which produced a urinary solute load of about 600 mosM per m^2 per 24 hours, he needed about 9000 ml of solute free water to cover urinary needs plus 1000 to equalize extrarenal water losses or a total of about 10,000 ml per m^2 per 24 hours (chart 47A and column *a* of left-hand division of chart 47B) This requirement could be lessened only by reducing the solute content of his diet, the effects of lowering his urinary load to 400 or to 200 mosM per m^2 per 24 hours are indicated by columns *b* and *c* of the left hand division of chart B In all other respects, his renal function appeared to be well developed (charts 47A, B)

Such an isolated congenital defect in homeostatic function can have far reaching effects on body economy (chart 47C) For instance, when this child was taking whole cow's milk, he needed on the average to drink every 24 minutes and to void every 50 minutes Since he awoke for each of these activities, the duration of uninterrupted sleep was never greater than about 20 minutes This made it impossible for him to fulfill his sleep requirements at night and hence necessary for him to nap intermittently during the day As a result, there was little opportunity for social contact, play and learning The clinical manifestation of this was gross retardation in mental and emotional development

When the solute load was reduced by substitution of an isocaloric dilute formula made up by mixing equal parts of whole cow's milk and 15 per cent dextrose in water, the rate of water turnover slowed so much that he could go for about 66 minutes without drinking or voiding Fol lowing this change, his daily pattern of activities became almost normal for a child of his age and he commenced to grow and mature physically, intellectually and emotionally at a markedly accelerated rate

* Intravenous administration of a test dose of 2 units of aqueous posterior pituitary extract per m^2 failed to produce a normal fall in urine water solute ratio to levels of approximately 2 ml per mosM



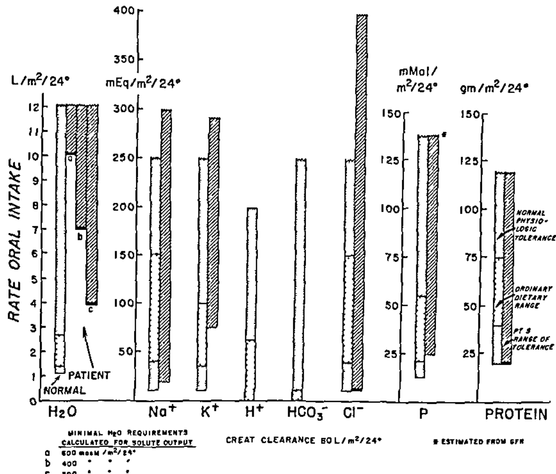
47A. Nephrogenic Diabetes Insipidus of the Pitressin-resistant Type

The body surface of this 2½-year-old patient was estimated to be 0.45 m². The design of the chart corresponds to that of chart 45A.

It is interesting to note that he derived about as much benefit *in terms of his activity pattern* from this dilute formula regimen, which was compatible with normal growth and development, as he did from the much more drastic nutritionally inadequate dextrose and water regimen.

References

Hillman *et al* (1958) General and source of data chart 47C
Waring *et al* (1945) General



47B. Tolerance of a Child with Nephrogenic Diabetes Insipidus as Defined by Data of Chart 47A

Note in the left-hand section that the patient's minimal water requirements are set forth relative to rates of solute output The design of the chart corresponds to that of chart 45B.

Percent of observation periods		Average values for: Fluid intake			Average values for: Urine output		
	Activity of patient	Volume per hour ml	Interval between drinks min	Volume per drink ml	Volume per hour ml	Interval between voidings min	Volume per voiding ml
Whole cow's milk	Sleep (51%), Drink (28%), Play (21%)	247	24	120	135	50	112
Dilute formula	Sleep (45%), Drink (6%), Play (49%)	120	66	141	77	66	102
Dextrose & water	Sleep (37%), Drink (7%), Play (56%)	89	66	127	74	90	132
	Activity of normal 15 mo 12 kg						
Whole cow's milk	Sleep (29%), Drink (7%), Play (64%)	50	288	240	25	240	100

47C. Effects of Limitation in Capacity to Conserve Water Due to Pitressin Resistance

The chart shows the daily life pattern of the patient a 15 month-old infant weighing 6.6 kg while taking (a) whole cow's milk (b) a dilute low solute formula and (c) a solute free dextrose in water solution These patterns may be compared with those of a normal infant of similar age shown at the bottom of the chart. From Hillman *et al* (1958)

REFERENCES

GAMBLE, J L *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid A Lecture Syllabus* (6th ed) Harvard Univ Press, Cambridge, 1958

GAMBLE, J L, WALLACE, W M, ELIEL, L, HOLLIDAY, M A, CUSHMAN, M, APPLETON, J, SHENBERG, A, and PIOTTI, J Effects of large loads of electrolytes, *Pediatrics* 7 305, 1951

GARDNER, L I, MAC LACHLAN, E A, PICK, W, TERRY, M L, and BUTLER, A M Etiologic factors in tetany of newly born infants, *Pediatrics* 5 228, 1950

GINANDES, G J, and TOPPER, A Insensible perspiration in children II Statistical correlation of insensible perspiration and various body measurements, proposed basal standards for children, *Am J Dis Child* 52 1335, 1936

GOODMAN, L S, and GILMAN A Z *The Pharmacologic Basis of Therapeutics* (2nd ed) Macmillan, New York, 1955

HANSEN, D L, and SMITH, C A Effects of withholding fluid in the immediate postnatal period, *Pediatrics* 12 99, 1953

HEELEY, A M, and TALBOT, N B Insensible water losses per day by hospitalized infants and children, *Am J Dis Child* 90 251, 1955

HILLMAN, D A, NEYZI, O, PORTER, P, CUSHMAN, A, and TALBOT, N B Renal (vasopressin resistant) diabetes insipidus, definition of the effects of a homeostatic limitation in capacity to conserve water on the physical, intellectual and emotional development of a child, *Pediatrics* 21 430, 1958

KERRIGAN, G A, TALBOT, N B and CRAWFORD, J D Role of the neurohypophyseal antidiuretic-hormone renal system in everyday clinical medicine, *J Clin Endocrinol* 15 265, 1955

KETY, S S, and SCHMIDT, C F The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men, *J Clin Invest* 27 484, 1948

LARAGH, J H, and STOERK, H C A study of the mechanism of secretion of the sodium retaining hormone (aldosterone), *J Clin Invest* 36 383, 1957

LEAF, A, COUTER, W T, and NEWBURGH, L H Some effects of variation in sodium intake and of different sodium salts in normal subjects, *J Clin Invest 28 1082, 1949*

LEAF, A, BARTTER, F C, SANTOS, R F, and WRONG, O Evidence in man that urinary electrolyte loss induced by pitressin is a function of water retention, *J Clin Invest* 32 868, 1953

LEVINE, S Z, KELLY, M, and WILSON, J R The insensible perspiration in infancy and children II Proposed basal standards for infants, *Am J Dis Child* 39 917, 1930

LOWE, C U: Practical thoughts on electrolyte and fluid administration, *Pediatrics* 15.498, 1955
LUND, C. C, and BROWDER, N C. The estimation of areas of burns, *Surg, Gynec & Obst* 79 352, 1944

MACY, I G *Nutrition and Chemical Growth in Childhood* Vol I *Evaluation* Thomas, Springfield, Ill, 1942
MC CANCE, R A, and WIDDOWSON, E M Hypertonic expansion of the extracellular fluids, *Acta Pediat* 46 337, 1957
MOORE, F D Common patterns of water and electrolyte change in injury, surgery, and disease, *New England J Med* 258 277, 325, 377, 427, 1958
MOORE, F. D, and BALL, M R *The Metabolic Response to Surgery* Thomas, Springfield, Ill, 1952

NABARRO, J D N, SPENCER, A G, and STOWERS, J M Metabolic studies in severe diabetic ketosis, *Quart J Med* 21 225, 1952
NELSON, W E (ed) *Textbook of Pediatrics* (6th ed) Saunders, Philadelphia, 1954
NEWBURGH, L H, JOHNSTON, M W, and NEWBURGH, J D *Some Fundamental Principles of Metabolism* Edwards Bros, Ann Arbor, 1945
NEYZI, O, BAILEY, M, and TALBOT, N B Effects of varying infusion time in maintenance fluid therapy, *New England J Med* 258 1239, 1958
NICHOLS, G, JR, NICHOLS, N, WEIL, W B, and WALLACE, W M The direct measurement of the extracellular phase of tissues, *J Clin Invest* 32 1299, 1953
NICHOLSON, T F The mode and site of the renal action of parathyroid extract in the dog, *Canadian J Biochem & Physiol* 37 113, 1959
NICHOLSON, T F, and SHEPHERD G W The effect of damage to various parts of the renal tubule on the excretion of phosphate by the dog's kidney, *Canadian J Biochem & Physiol* 37 103, 1959

OLIVER, W J, GRAHAM, B D, and WILSON J L Lack of scientific validity of body surface as basis for parenteral fluid dosage, *J A M A* 167 1211, 1958
ORLOFF, J The role of the kidney in the regulation of acid base balance, *Yale J Biol & Med* 29 211, 1956

PITTS, R F Renal excretion of acid *Fed Proc* 7 418, 1948
PITTS, R F, AYER, J L, and SCHIESS W A The renal regulation of acid base balance in man III The reabsorption and excretion of bicarbonate, *J Clin Invest* 28 35, 1949

TALBOT, N B, SOBEL, E H, MC ARTHUR, J W, and CRAWFORD J D *Functional Endocrinology from Birth through Adolescence* Harvard Univ Press, Cambridge, 1952

TALBOT, N B, CRAWFORD, J D, and BUTLER, A M Homeostatic limits to safe parenteral fluid therapy, *New England J Med* 248 1100, 1953

TALBOT, N B, KERRIGAN, G A, CRAWFORD, J D, COCHRAN, W, and TERRY, M L Application of homeostatic principles to the practice of parenteral fluid therapy, *New England J Med* 252 856, 898, 1955

TALBOT, N B, CRAWFORD, J D, KERRIGAN, G A, HILLMAN, D, BERTUCIO, M, and TERRY, M L Application of homeostatic principles to the management of nephritic patients, *New England J Med* 255 655 1956

TALBOT, N B, CRAWFORD J D and COOK, C D Application of homeostatic principles to the management of nephrotic patients, *New England J Med* 256 1080, 1957

TALBOT, N B, and RICHIE R The effect of age on the body's tolerance for fasting, thirsting and for overloading with water and certain electrolytes, *Ciba Foundation Colloquia on Ageing* 4 139, 1958

TALBOT, N B, and RICHIE, R The advantages of surface area as a common denominator in calculating pediatric dosages *Pediatrics* (in press), 1959

VERNEY, E B Renal excretion of water and salt *Lancet* 2 1237, 1957

WARING, A J, KAJDI, L, and TAPPAN V A congenital defect of water metabolism, *Am J Dis Child* 69 323, 1945

WEIL, W B, and WALLACE, E M Hypertonic dehydration in infancy, *Pediatrics* 17 171, 1956

WINKLER, A W, HOFF, H F, and SMITH P K Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride *Am J Physiol* 124 478 1938

WYNN, V Water intoxication and serum hypotonicity, *Metabolism* 5 490, 1956